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(54) Title: MODULATION OF NUCLEAR RECEPTORS ACTIVITY

(57) Abstract: The present invention relates to specific compounds and pharmaceutically acceptable salts thereof; methods for synthesizing these compounds; compositions comprising at least one of these compounds or a pharmaceutically acceptable salt thereof; and methods for modulating liver-X receptors (LXRs) activity. The present invention further concerns methods for treating and/or preventing a disease or disorder selected from the group consisting of dyslipidemia, including hyperlipidemia, dyslipoproteinemia, including hyperlipoproteinemia, disorders related to cholesterol or bile acid metabolisms, including hypercholesterolemia, gall stone or gall bladder disorders, cardiovascular disease, including atherosclerotic cardiovascular diseases, coronary artery diseases, peripheral vascular diseases, cerebrovascular diseases, thrombotic disorders, restenosis or septic shock, CNS diseases including those affecting cognitive function or age related disorders such as Alzheimer's disease, Syndrome X, a liver-X receptor-associated disorder, obesity, pancreatitis, hypertension, renal disease, cancer, rheumatoid arthritis, inflammation, skin proliferative disorders, including psoriasis, atopic dermatitis or acne, and sexual impotence, comprising administering a therapeutically effective amount of a composition comprising at least one compound or a pharmaceutically acceptable salt thereof of the invention.

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MODULATION OF NUCLEAR RECEPTORS ACTIVITY

The present invention relates to specific compounds and pharmaceutically acceptable salts thereof; methods for synthesizing these compounds; compositions comprising at least one of these compounds or a pharmaceutically acceptable salt thereof; and methods for modulating liver-X receptors (LXRs) activity. The present invention further concerns methods for treating and/or preventing a disease or disorder selected from the group consisting of dyslipidemia, including hyperlipidemia, dyslipoproteinemia, including hyperlipoproteinemia, disorders related to cholesterol or bile acid metabolisms, including hypercholesterolemia, gall stone or gall bladder disorders, cardiovascular disease, including atherosclerotic cardiovascular diseases, coronary artery diseases, peripheral vascular diseases, cerebrovascular diseases, thrombotic disorders, restenosis or septic shock, CNS diseases including those affecting cognitive function or age related disorders such as Alzheimer's disease, Syndrome X, a liver-X receptor-associated disease or disorder, obesity, pancreatitis, hypertension, renal disease, cancer, rheumatoid arthritis, inflammation, skin proliferative disorders, including psoriasis, atopic dermatitis or acne, and sexual impotence, comprising administering a therapeutically effective amount of a composition comprising at least one compound or a pharmaceutically acceptable salt thereof of the Invention.

The following description is provided to aid in understanding the invention but is not admitted to be prior art to the invention.

Lipoproteins are macromolecular complexes formed among others by lipids (e.g. cholesterol and/or triglycerides) and apolipoproteins (e.g. apolipoproteins A, B, C and/or E) that allow lipids to circulate, especially in the blood. These particles can be classified according to their density into several groups, namely the chylomicrons (density < 0.94 g/mL) which are mainly containing triglycerides (TG), the Very Low Density Lipoproteins (VLDL ; d = 0.94-1.006 g/mL) carrying mainly TG with some cholesterol, the Intermediate Density Lipoproteins (IDL ; d = 1.006-1.019 g/mL) formed from the catabolism of VLDL and enriched in cholesterol, the Low Density Lipoproteins (LDL ; d = 1.019-1.063 g/mL) which are rich in cholesterol and rich in TG, and the High Density Lipoproteins (HDL ; d > 1.063 g/mL) which are very rich in cholesterol. Functionally, LDL particles (noted LDL) are responsible for the delivery of cholesterol from the liver (where it is synthesized or obtained from dietary sources) to extrahepatic tissues in the body, while HDL particles (noted HDL) play a major role in the transport of cholesterol from peripheral tissues to the liver (i.e. "reverse cholesterol transport" or RCT) where it is catabolized and eliminated.

Disorders of lipid metabolism, or dyslipidemias, are described in terms of elevation of lipid (cholesterol and/or triglycerides) in general (i.e. total cholesterol and/or triglyceride levels), and more specifically in lipoprotein particles LDL, IDL and VLDL, or reduction in cholesterol carried in HDL. For example, the National Cholesterol Education Program (NCEP) has defined as abnormal lipid and lipoprotein cholesterol values, a low-density lipoprotein cholesterol (LDL-c) value of 160 mg/dL (4.1 mmol/L) or greater, a high-density lipoprotein cholesterol (HDL-c) value less than 40 mg/dL (1.0 mmol/L), triglycerides (TG) 150 mg/dL

(1.7 mmol/L) or greater, and a lipoprotein a (Lpa) of 30 mg/dl or greater.

Although there is debate about the strength of the association between some forms of dyslipidemia and the risk of developing cardiovascular disease, the evidence exists that the reduction in cholesterol, and potentially triglyceride, in LDL-c and/or VLDL-c leads to a reduction in coronary heart disease mortality and morbidity (for a review, e.g., see Superko et al., 2002, Prog. Cardiovasc. Nurs., 17, 167-73). The strongest link with atherosclerosis, which is a slowly progressive disease characterized by the accumulation of cholesterol within the arterial wall, exists for elevated concentrations of LDL-c and clinical data support the benefits of aggressive therapy leading to an LDL-c lowering in appropriate populations (this is the reason why LDL-c is commonly called the "bad" cholesterol)(e.g., Desager et al., 1996, Atherosclerosis, 124, S65-S73). Moreover, epidemiological data have reaffirmed that elevated plasma triglyceride and low HDL-c levels are also important independent risk factors for atherosclerotic vascular disease (for a review, e.g., Rader, 2002, Am. J. Cardiol., 90, 62i-70i). HDL being implicated in the transport of cholesterol from peripheral tissues to the liver, low concentrations of HDL-c as a percentage of total plasma cholesterol may lead to a failure to efficiently export lipid from the vessel wall, leading to atherosclerotic plaque development, and hence increased cardiovascular risk. Clinical data have shown that there is a 2% to 3% decrease in coronary risk for each 1 mg/dL increase in HDL-c, thus it is commonly called the "good" cholesterol. Additionally, it is hypothesized that high levels of plasma HDL-c are not only protective against coronary artery disease, but may actually induce regression of atherosclerotic plaques (e.g., Libby, 2001, Am. J.

Cardiol., 88, 3N-8N ; for a review, see Eckardstein et al., 2001, Arterioscler. Thromb. Vasc. Biol., 21, 13-27).

The metabolic pathways of lipoproteins, cholesterol and triglycerides are reviewed for example in Kwiterovich, 2000, Am. J. Cardiol., 86, 5L-10L. Cholesterol is essential in the synthesis of cell membranes, bile acids and steroid hormones while triglycerides are important to peripheral tissue as a source of energy production. Although the liver is the major site of cholesterol biosynthesis, cholesterol and triglycerides from the diet can also be absorbed from the intestine and transported in the form of chylomicrons. The chylomicrons transport cholesterol and triglycerides from the intestine to, respectively, the adipose tissue for storage and to the liver for packaging and resecretion as VLDL or LDL particles. After extensive hydrolysis of triglycerides, the remaining particles, i.e. chylomicron remnants, are taken up by the liver. Prolonged uptake of these triglycerides particles (VLDL or chylomicron remnants) by the liver can lead to reduced hepatic production of LDL receptors (LDLr) and to increases in plasma cholesterol levels. Hydrolysis of triglyceride-rich particles in the liver leads to release of free fatty acids. Fatty acids not used for energy generation by the liver are converted to triglycerides for hepatic storage or packaged into VLDL particles along with cholesterol to be transported to the peripheral tissues. The VLDL particles are hydrolyzed *via* the lipoprotein lipase (LPL) to form IDL particles. The liver takes up about 60% of the IDL *via* the LDLr and the remainder is hydrolyzed by the hepatic lipase (HL) to produce LDL particles. The major role of LDL is to transport cholesterol to the peripheral tissues. When intracellular cholesterol is required, cells may synthesise cholesterol, or acquire exogenous cholesterol through upregulation of LDLr resulting in the increased uptake of LDL-c. The LDLr is responsible for removing 60 to

80% of the LDL particles. Increased intracellular cholesterol inhibits the activity of HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, and decreases the synthesis of LDLr in order to limit the further uptake of cholesterol into the cell. LDL-c can be modified, e.g. by oxidation, leading to decreased recognition by the LDLr, increased circulation time in the plasma and increased uptake of modified LDL-c by scavenger receptors on macrophages. This leads to the accumulation of cholesterol and lipids in tissue macrophages, and consequently leads to the establishment of atherosclerotic plaques in the arterial system.

HDL is regarded as essential for reverse cholesterol transport (RCT), i.e. the removal of cholesterol from peripheral tissue and its transport back to the liver. Nascent HDL (pre beta-HDL) are synthesized in the liver and small intestine and enter the plasma compartment. When pre beta-HDL particles come in contact with cells rich in cholesterol, there is a transfer of cholesterol to the particle by cell surface proteins such as the ATP-binding cassette transporter 1 (ABCA-1) which are responsible for the efflux of cholesterol from cells into the plasma. Once transferred to HDL, the free cholesterol is esterified by the lecithin-cholesterol acyltransferase (LCAT) and the resulting cholesteryl esters (CE) are incorporated into the lipid core of the HDL particle allowing it to increase in size and mature into HDL_3. Further addition of CE results in the maturation to HDL_2. HDL_2 may (i) deliver cholesterol to the liver through interactions with hepatic HDL receptors (also called SR-B1) and be converted back to HDL_3; (ii) exchange lipids with other lipoprotein classes through Cholesteryl Ester Transfer Protein (CETP) mediated transfer; or (iii) be taken up as a whole by the liver.

A number of treatments are currently available for attempting both to reduce plasma LDL-c and VLDL-c (that is

reduce total plasma cholesterol) and/or triglycerides, and advantageously to increase the HDL-c fraction of total plasma cholesterol (see Gotto, 2002, Am. J. Med., 112 Suppl 8A, 10S-18S). Besides therapies based on a low fat diet and elimination of aggravating factors such as a sedentary lifestyle or smoking, several classes of drugs are routinely used in the treatment of simple hypercholesterolemia (SH), mixed dyslipidemia (MD) and hypertriglyceridemia (HTG)/low HDL-c, however, each has its own drawbacks and limitations in terms of efficacy, side-effects and qualifying patient populations :

(i) statins, which are inhibitors of 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (the rate-limiting enzyme in cholesterol biosynthesis), are the most widely prescribed drug class for the treatment of hypercholesterolemia. Examples of statins are mevastatin, lovastatin (Mevacor™, Merck), pravastatin (Pravachol™, Sankyo / Bristol-Myers Squibb) and simvastatin (Zocor™, Merck). Examples of synthetic statins are fluvastatin (Lescol™, Novartis), atorvastatin (Lipitor™, Pfizer) and rosuvastatin (Crestor™, AstraZeneca), cerivastatin (Baycol™, Bayer) and pitavastatin. This class of drugs significantly reduces TG (10-37%), total cholesterol (15-45%), LDL-c (20-50%), but with only a modest (2-12%) increase in HDL-c concentrations. However, benefits from these therapies not only vary from subject to subject, but is additionally associated with side effects. Most of the known adverse effects are directly related to their biochemical mechanism of action and are the result of potent and reversible inhibition of an enzyme involved in cellular homeostasis (e.g., Gerson et al., 1989, Am. J. Med., 87, 28S-38S). The most common adverse effects are of gastrointestinal origin, with the occurrence of nausea, bloating, diarrhea or constipation, but they further include liver dysfunction and various form of myopathy (e.g.,

Sinzinger et al., 2000, Atherosclerosis, 153, 255-256). Additionally, in severe forms of hypercholesterolemia, statins are not efficacious enough as monotherapy to normalize lipid levels and thus require combination therapy (e.g. with ezetimibe).

(ii) fibric acid derivatives (fibrates) affect the expression of genes implicated in the regulation of HDL and TG-rich lipoproteins as well as fatty acid metabolism via the activation of the peroxisome proliferator-activated receptor alpha (PPAR-alpha). The current fibrates are all low potency PPAR-alpha agonists (i.e., they require high micromolar concentrations for receptor activation), which may explain why high doses are required for their clinical activity. Clofibrate and gemfibrozil are two of the oldest known fibrates, while bezafibrate, fenofibrate and ciprofibrate illustrate the second generation. The new fibrates reduce TGs (20-60%) and increase HDL-c (10-35%), however, the effects of these drugs on serum cholesterol are variable and it is not always possible to predict which patients will benefit from treatment. Moreover, while prevention of coronary heart disease was observed in male patients between 40-55 without history or symptoms of existing coronary heart disease, it is not clear to what extent these findings can be extrapolated to other patient populations (e.g., women, older and younger males). Indeed, no efficacy was observed in patients with established coronary heart disease. In the United States, fibrates have been approved for use as hypolipidemic drugs, but have not received approval as hypercholesterolemia agents. Additionally, serious side-effects are associated with the use of fibrates including toxicity such as malignancy (e.g. gastrointestinal cancer), gallbladder disease and an increased incidence in non-coronary mortality. Other side effects are nausea, diarrhea, indigestion, headache, loss of libido, skin rash, and drowsiness occurs

less frequently. Toxicological studies have shown that the liver, muscle and kidney are potential target organs and tissues. Moreover, the fibrates are contraindicated in pregnant or lactating women, or patients with severe liver or renal impairment or existing gallbladder disease.

(iii) bile acid sequestrants (BAS) / cholesterol absorption inhibitors. The bile acid sequestrants (anion-exchange resins) are non-systemic drugs acting by binding bile acids within the intestinal lumen, thus interfering with their re-absorption and enhancing their fecal excretion. This leads to the increased hepatic conversion of cholesterol to bile acid *via* upregulation of cholesterol 7beta-hydroxylase activity. The liver's increased requirement for cholesterol is partially met through an increased hepatic removal of circulating LDL-c *via* up-regulation of hepatic LDL receptors. Examples are cholestyramine, which is a copolymer of polystyrene and divinylbenzene or colestipol which is the hydrochloride salt of a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane. Both cholestyramine and colestipol are effective cholesterol-lowering drugs in monotherapy as well as in combination with statins, fibrates, niacin or probucol (see below), however, the BAS use is limited due to the need of large doses to achieve efficacy and their side effect profile (i.e. gastrointestinal side-effects, including constipation and certain vitamin deficiencies), as well as to the possible interactions with other drugs such as for example aspirin, clindamycin, fibrates, nicotinic acid, warfarin, etc... Recently, colesevelam, a third generation bile acid sequestrant with increased *in vitro* potency, has shown similar LDL-lowering efficacy at much lower doses without the side effects associated with the other bile acid sequestrants. However, the use of colesevelam is limited to the treatment of persons with moderate hypercholesterolemia (e.g., Davidson et al, 1999, Arch. Intern. Med., 159, 1893-

1900). Ezetimibe (Zetia™, Schering-Plough) is a cholesterol absorption inhibitor preventing the absorption of cholesterol by inhibiting the transfer of dietary and biliary cholesterol across the intestinal wall.

(iv) nicotinic acid (niacin) derivatives reduce TG (20-50%), total cholesterol (10-15%), LDL-c (10-20%), and cause a significant increase in HDL-c concentrations (10-30%). However, its utility is limited because of very poor patient compliance as niacin is not very well tolerated. Nearly all patients suffer from serious side effects, including itching, flushing and gastrointestinal intolerance. Additionally, current guidelines do not recommend the use of niacin in patients with diabetes because it can exacerbate gout and worsen glycemic control.

(v) Probucol was discovered as a lipid-lowering agent in 1964 from a screening program of phenolic antioxidants. Its exact mode of action is unclear but it has been shown to reduce both LDL-c (8-15%) and HDL-c (by as much as 40%) and thus, due to the decrease in HDL-c and other side effects (gastrointestinal side effects include diarrhea, flatulence, abdominal pain, nausea and vomiting), probucol is rarely used in the treatment of hyperlipidemia. Ultimately, it was withdrawn from the United State market because of its potential to induce serious ventricular arrhythmias.

(vi) Hormone Replacement Therapy (HRT). The use of HRT, estrogen and progesterone, in post-menopausal women has increased dramatically over the last 10 years. Not only has HRT shown benefit for the treatment of postmenopausal symptoms but also in several studies, a reduction in the number of cardiovascular events was observed. HRT directly stimulates LDL receptor activity, leading to the reduction in total cholesterol and LDL-c levels, moderate increases in HDL-c levels which unfortunately may be accompanied with an

increase in triglycerides. HRT in combination with a statin has also shown to be very effective in lowering LDL-c levels. However, HRT is associated with side effects including an increased relative risk of breast and endometrial cancer with each year of treatment, as well as a risk of venous and pulmonary thromboembolism and possibly with ovarian cancer, induction of gall bladder disease, thromboembolic disease, hepatic adenoma, elevated blood pressure, glucose intolerance, and hypercalcemia.

(vii) estrogen modulators, such as tamoxifen, toremifene and raloxifene, are used in postmenopausal women in the treatment of breast cancer and in the prevention of osteoporosis. All these drugs have been demonstrated to further reduce total cholesterol and LDL-c. Unlike HRT, tamoxifen, toremifene and raloxifene have been shown not to increase the risk of breast and endometrial cancer.

(viii) Plant sterols and stanols inhibit the intestinal absorption of cholesterol and as a result lower plasma LDL-c concentrations. They are found, in varying degrees, naturally in almost all vegetables. The most abundant of the phytosterols is beta-sitosterol and the fully saturated derivative of beta-sitosterol is sitostanol. Plant sterols are absorbed to a small extent while plant stanols are virtually non-absorbable. Thus, intestinal levels of stanols will be prolonged compared to that of sterols, which may explain why plant stanols appear to be more effective in decreasing cholesterol absorption and reducing serum LDL levels. Plant stanols have also been shown to reduce serum cholesterol levels in patients on statin therapy. Sterol and stanol esters can be used as food additives to allow adequate amounts to be consumed without affecting food quality or dietary habits. Low fat stanol or sterol ester-containing margarines in combination with a low fat diet have been shown to reduce LDL-c levels in hypercholesterolemic subjects.

Unless consumed at extraordinarily high levels, practically no side effects have been observed.

There was thus a need to develop new and safer drugs and methods that are efficacious in lowering serum cholesterol, increasing HDL-c serum levels, treating and/or preventing a disease or disorder associated, directly or indirectly, with dyslipidemia, dyslipoproteinemia and/or disorders related to cholesterol metabolism such as for example coronary heart disease, lipid storage diseases, e.g. atherosclerosis and obesity, diabetes, etc. Thus, additional strategies have been proposed, among which is the modulation of the activity of liver-X receptors (LXRs) and, in turn, the control of the delicate balance of cholesterol metabolism and fatty acid biosynthesis (e.g. Edwards, 2002, J. Lipid Res., 43, 2-12 ; Repa and Mangelsdorf, 2002, Nature Medicine, 8, 1243-1248).

The liver X receptors (LXR-alpha, NR1H3, and LXR-beta, NR1H2) are members of the nuclear hormone receptor superfamily of ligand-activated transcription factors. These proteins contain a central DNA-binding domain consisting of two zinc-finger motifs and a large ligand-binding domain with a lipophilic core that specifically binds small lipid molecules such as naturally occurring oxidized derivatives of cholesterol, including 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and 24,25(S)-epoxycholesterol (see, Lehmann, et al., 1997, J. Biol. Chem., 272, 3137-3140). After ligands have bound, the nuclear receptors undergo a change in conformation that promotes interactions with co-activator proteins (cofactors) that facilitate transcription of cognate target genes. LXR-alpha is highly expressed in liver, and is also found in adipose, intestine, kidney and macrophages. LXR-beta expression is detectable in nearly every tissue examined. Several cholesterol homeostasis-related genes have been identified as direct LXRs target genes, e.g., ATP-binding cassette transporters A1 (ABCA1), G1 (ABCG1), G5

(ABCG5) and G8 (ABCG8), cholesterol 7-alpha-hydroxylase (CYP7A1 ; in mouse), phospholipid transfer protein (PLTP), cholesteryl ester transfer protein (CETP), Apolipoprotein E (ApoE), stearoyl CoA desaturases1 and 2 (Scd1, Scd2) (Sun et al., J. Biol. Chem. 2002 Dec 12; accepted manuscript published on the Medline website M208687200), lipoprotein lipase (LPL), acetyl-CoA carboxylase (ACC) (Liang et al., 2002, J. Biol. Chem., 277, 9520-9528), Fatty acid synthase (FAS) (Liang et al., 2002, supra) and sterol regulatory element-binding protein-1c (SREBP-1c) (e.g., see Repa and Mangelsdorf, 2002, Nature Medicine, 8, 1243-1248). Joseph et al. (2002, Proc. Natl. Acad. Sci., 99, 7604-7609) have shown that LXRs exert an important atheroprotective effect in macrophages and that systemic administration of an LXR agonist reduced atherosclerosis in mouse models. More recent studies have further demonstrated that activation of the LXR pathway antagonizes inflammatory gene expression and reduces inflammation, thus raising the possibility that LXR agonists have utility in the treatment of other chronic inflammatory diseases (Joseph et al., 2003, Nat. Med., 9, 213 - 219). Finally, several groups have shown that while LXR-alpha and LXR-beta share a high degree of amino acid identity and bind endogenous oxysterol ligands with similar affinities, they activate distinct target genes and thus their respective activation can result in distinct *in vivo* pharmacological effects, especially in the context of lipid metabolism.

The LXRs, especially LXR-alpha, have been shown to be exciting new targets for the development of therapeutic compounds that by modulating LXRs activity are likely to have utility at least in the treatment and/or prevention of diseases or disorder that are associated, directly or indirectly, with dyslipidemia, dyslipoproteinemia and/or disorders related to cholesterol metabolism, as well as vascular or inflammatory diseases or disorders, or diseases

or disorders associated with deficiency of at least one LXRs target gene expression. Examples of LXRs modulating compounds are provided, e.g., in US20020193357, US20020048572, US6316503, WO0224632, WO0054759, WO0103705. Two specific identified LXRs modulating compounds are T0901317 (compound 12 of WO0054759) and GW3965 which can be used as reference compounds. T0901317 or (*N*-(2,2,2-trifluoro-ethyl)-*N*-[4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-phenyl]-benzenesulfonamide) is a synthetic, nonsteroidal LXR-selective agonist presenting a high affinity towards LXR alpha (EC_{50} values of 20 nM) and beta (Schultz et al., 2000, Genes Dev. 14, 2831-2838). It possesses the capacity to activate LXRs *in vitro* during the transfection assays, to induce the cholesterol efflux *in vitro* (Laffitte et al., 2001, Mol Cell Biol. 21, 7558-7568) and to improve insulin sensitivity in diabetic animals (Cao et al., 2003, J Biol. Chem. 278, 1131-1136.). In addition, T0901317 possesses the capacity to induce lipogenesis *in vitro and in vivo* (Schultz, et al., 2000, Genes Dev. 14, 2831-2838; Joseph, et al., 2002, J. Biol. Chem. 277, 11019-11025). GW3965 is a synthetic high affinity LXR alpha and beta ligand (Collins, et al., 2002, J. Med. Chem. 45, 1963-1966) that possesses the capacity to activate LXRs *in vitro* during the transfection assays, to induce both the cholesterol efflux *in vitro* and *in vivo* (Collins, et al., 2002, J. Med. Chem., 45, 1963-1966) and to inhibit the development of atherosclerosis in atherosclerotic animal models (Joseph, et al., 2002, Proc. Natl. Acad. Sci. 99, 7604-7609). In addition, GW3965 possesses the capacity to induce lipogenesis *in vivo* (Joseph, et al., 2002, Proc. Natl. Acad. Sci. , 99, 7604-7609).

However, Schultz et al., 2000, Gene and Dev., 14, 2831-2838 have further shown that LXR agonists may have pharmacologic effects that are both desirable (e.g. increased reverse cholesterol transport) and undesirable (e.g.

activation of lipogenesis resulting in hypertriglyceridemia). More recently, Inaba et al. (2003, J. Biol. Chem., 278, 21344-51) have further demonstrated that the gene encoding angiopoietinlike protein 3 (Angptl3), a liver-specific secretory protein, is a direct target of LXR and that its induction accounts for hypertriglyceridemia associated with the treatment of LXR ligands. Accordingly, while the responses observed in the context of these various treating and/or preventing methods, are encouraging, none are yet fully satisfactory treatments.

The general problem underlying the invention is to develop new modulators of the LXRs activity. The Applicant has now identified compounds of general formula (I) and/or (II) below, their derivatives, their analogues, their pharmaceutically acceptable solvates or salts and pharmaceutical compositions containing them or mixtures thereof.

Another objective of the present invention is to provide compounds of the general formula (I) and/or (II) and their derivatives, their analogues, their pharmaceutically acceptable solvates or salts and pharmaceutical compositions containing them or mixtures thereof, which may have agonist activity against LXRs. In special embodiment, said agonist presents a partial agonist activity against LXRs.

Another objective of the present invention is to provide compounds of the general formula (I) and/or (II) and their derivatives, their analogues, their pharmaceutically acceptable solvates or salts and pharmaceutical compositions containing them or mixtures thereof having enhanced activities towards LXRs without undesirable effects or with reduced undesirable effects.

Yet another objective of the present invention is to provide a process for the preparation of compounds of the

general formula (I) and/or (II) and their derivatives, their analogues, their pharmaceutically acceptable solvates or salts.

Still another objective of the present invention is to provide compositions containing compounds of the general formula (I) and/or (II), their derivatives, their analogues, their pharmaceutically acceptable solvates or salts or their mixtures in combination with suitable pharmaceutical carriers, solvents, diluents and other media normally employed in preparing such compositions.

Still another objective of the present invention is to provide methods which use the compounds or compositions of the Invention as the active ingredient for the treatment and/or prophylaxis of various diseases and conditions which can be, at least partially, controlled by LXRs, including metabolic or cell proliferative disorders such as, for example, diseases and conditions related to pathologic levels or ratios of lipids (e.g. dyslipidemia, including hyperlipidemia, dyslipoproteinemia, including hyperlipoproteinemia, disorders related to cholesterol or bile acid metabolisms, including hypercholesterolemia, gall stone or gall bladder disorders) ; as well as vascular or inflammatory diseases or disorders (e.g. cardiovascular disease, including atherosclerotic cardiovascular diseases, coronary artery diseases, peripheral vascular diseases, cerebrovascular diseases, thrombotic disorders ,restenosis, rheumatoid arthritis, or septic shock); diseases or disorders associated with malfunctioning (including deficiency) of the expression of at least one LXRs target gene; CNS diseases including those affecting cognitive function or age related disorders such as Alzheimer's disease ; diseases or disorders related to lipid storage such as obesity, diabetes (including type 2 diabetes), hypertension ; skin proliferative

disorders, including psoriasis, atopic dermatitis or acne ; sexual impotence, renal disease and cancers.

Still another objective of the present invention is to provide methods which use the compounds or compositions of the Invention as the active ingredient for lowering one or more of the following biological entities in the treated patient: triglycerides, fatty acids, total cholesterol, LDL-c, VLDL-c, bile acid and the like.

Still another objective of the present invention is to provide methods which use the compounds or compositions of the Invention as the active ingredient for increasing the HDL-c level.

Another objective of the present invention is to provide methods which use the compounds or compositions of the Invention as the active ingredient for enhancing the Reverse Cholesterol Transport (RCT).

Another objective of the present invention is to provide methods of treatment and/or prophylaxis as above mentioned resulting, in the treated patient, in enhanced beneficial effects (e.g. lowering serum cholesterol, increasing HDL-c serum levels, enhancing RCT) without adverse effects or with reduced adverse effects, and especially with limited hypertriglyceridemia.

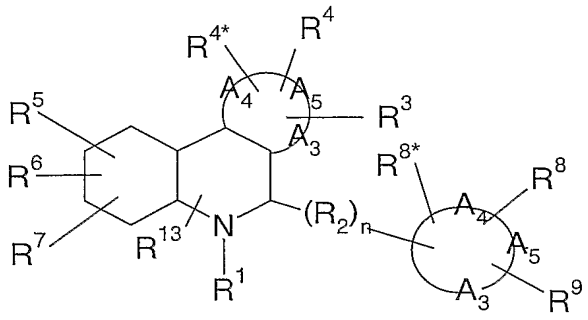
Further objectives will become apparent from reading the following description.

Throughout the specification, unless indicated differently, "LXRs" is intended to designate both LXR-alpha and/or LXR-beta without distinction. In preferred embodiments, it is designating LXR-alpha.

"HDL", "VLDL", "LDL" are intended to designate the lipoprotein particles as a whole, and "HDL-c", "VLDL-c",

"LDL-c" are intended to designate the cholesterol included in said particles, respectively.

According to a first embodiment, the present invention concerns compounds of the general formula (I):



or analogues, derivatives, solvates or salts thereof,

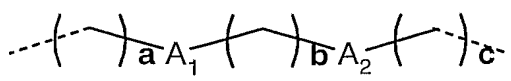
wherein :

R^1 is a moiety selected in the group consisting of -H, -Cl, -F, $-C_{n'}H_{2n'+1}$, $-CO-C_{n'}H_{2n'+1}$, $-O-C_{n'}H_{2n'+1}$, $-CO-O-C_{n'}H_{2n'+1}$, a cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety or a cycloheptyl), a $-(CH_2)_n-$ cycloalkyl moiety (e.g. a $-(CH_2)_n-$cyclohexyl or a $-(CH_2)_n$-phenyl moiety or a $-(CH_2)_n-$cycloheptyl), $-SO_2CF_3$, $-CF_3$, $-CO-CF_3$, $-O-CF_3$, $-(CH_2)_n-CF_3$, $-SO_2-(CH_2)_n-C_{n'}H_{2n'+1}$, ,$-SO_2-(CH_2)_n-$ cycloalkyl moiety (e.g. a $-SO_2-(CH_2)_n$-cyclohexyl or a $-SO_2-(CH_2)_n$-phenyl moiety) or $-SO_2-(CH_2)_n$-cycloheptyl), $-CO-(CH_2)_n-C_{n'}H_{2n'+1}$, $-CO-(CH_2)_n$-cycloalkyl moiety (e.g. a $-CO-(CH_2)_n$-cyclohexyl or a $-CO-(CH_2)_n$-phenyl moiety) or a $-CO-(CH_2)_n$-cycloheptyl);

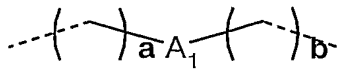
R^2 , R^{11} are, independently from one another, a moiety selected in the group consisting of :

(i) CH_2

(ii)



(iii)



with :

a, **b** and **c** are, independently from one another, an integer ranging from 0 to 4 ;

$\mathbf{A_1}$ and $\mathbf{A_2}$ are, independently from one another, a moiety selected in the group consisting of -CO-, -O-, $-SO_2-$, -CH-, $-CH_2-$, -NH-, $-N(C_{n'}H_{2n'+1})$, -N(cycloalkyl)- [e.g. -N(cyclohexyl)- or -N(phenyl)-] and -CHOH- ;

$\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^{4*}}$, $\mathbf{R^8}$, $\mathbf{R^{8*}}$, $\mathbf{R^9}$ are, independently from one another, a moiety selected in the group consisting of H, -Cl, $-CF_3$, -F, -Br, -CN, $-C_{n'}H_{2n'+1}$, a cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety or a cycloheptyl), $-(CH_2)_nCO_2H$, $-CH(CH_2)_2$, $-(CH_2)_n-CO-C_{n'}H_{2n'+1}$, $-(CH_2)_n-CO-$cycloalkyl (e.g. $-(CH_2)_n$ -CO-cyclohexyl or $-(CH_2)_n$ -CO-phenyl), $-(CH_2)_n-$cycloalkyl (e.g. $-(CH_2)_n-$cyclohexyl or $-(CH_2)_n-$phenyl), -OH, $-OCF_3$, $-OC_{n'}H_{2n'+1}$, $-O-(CH_2)_n-$ cycloalkyl (e.g. $-O-(CH_2)_n-$cyclohexyl or $-O-(CH_2)_n-$phenyl), $-O-(CH_2)_nCO_2H$, -COH, $-CO-C_{n'}H_{2n'+1}$, $-CO-(CH_2)_n-$cycloalkyl (e.g. $-CO-(CH_2)_n-$cyclohexyl or $-CO-(CH_2)_n-$phenyl), $-CO-(CH_2)_nCO_2H$, $-O-CO-(CH_2)_n-$cycloalkyl (e.g. $-O-CO-(CH_2)_n-$cyclohexyl or $-O-CO-(CH_2)_n-$phenyl), -O-benzoyl, $-SO_2H$, $-SO_2-C_{n'}H_{2n'+1}$, $-SO_2-(CH_2)_n-$ cycloalkyl (e.g. $-SO_2-(CH_2)_n-$cyclohexyl or $-SO_2-(CH_2)_n-$phenyl), $-SO_2-CO-(CH_2)_n-$ cycloalkyl (e.g. $-SO_2-CO-(CH_2)_n-$cyclohexyl or $-SO_2-$

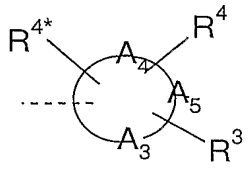
$CO-(CH_2)_n$-phenyl), $-SO_2-CO-$(cycloalkyl (e.g. $-SO_2-CO-$cyclohexyl or $-SO_2-CO-$phenyl), $-O-SO_2H$, $-O-SO_2-C_{n'}H_{2n'+1}$, $-O-SO_2-(CH_2)_n-$ cycloalkyl (e.g. $-O-SO_2-(CH_2)_n$-cyclohexyl or $-O-SO_2-(CH_2)_n$-phenyl), $-O-SO_2-CO-(CH_2)_n-$ cycloalkyl (e.g. $-O-SO_2-CO-(CH_2)_n$-cyclohexyl or $-O-SO_2-CO-(CH_2)_n$-phenyl), $-O-SO_2-CO-$(cycloalkyl (e.g. $-O-SO_2-CO-$cyclohexyl or $-O-SO_2-CO-$phenyl), $-NO_2$, $-NH_2$, $-NH(C_{n'}H_{2n'+1})$, $-N(C_{n'}H_{2n'+1})(C_{n'}H_{2n'+1})$, $-NH-(CH_2)_n-$cycloalkyl (e.g. $-NH-(CH_2)_n$-cyclohexyl or $-NH-(CH_2)_n$-phenyl), $-NH-CO-(C_{n'}H_{2n'+1})$, $-NH-CO-(CH_2)_n$-cycloalkyl (e.g. $-NH-CO-(CH_2)_n-$cyclohexyl or $-NH-CO-(CH_2)_n$-phenyl), $-NH-CO-$cycloalkyl (e.g. $-NH-CO-$cyclohexyl or $-NH-CO-$phenyl), $-SH$, $-SC_{n'}H_{2n'+1}$, $-S-(CH_2)_n-$cycloalkyl (e.g. $-S-(CH_2)_n$-cyclohexyl or $-S-(CH_2)_n-$phenyl), $-S-CO-(CH_2)_n-$ cycloalkyl (e.g. $-S-CO-(CH_2)_n-$cyclohexyl or $-S-CO-(CH_2)_n$-phenyl), $-S-CO-$(cycloalkyl (e.g. $-S-CO-$cyclohexyl or $-S-CO-$phenyl), $-(CH_2)_n-N(R^{10})(R^{10*})$, $-(CH_2)_n-CO-N(R^{10})(R^{10*})$, $-O-SO_2-N(R^{10})(R^{10*})$, $-CO-SO_2-N(R^{10})(R^{10*})$, $-SO_2-N(R^{10})(R^{10*})$, $-NR^{10}-SO_2CF_3$, $-NR^{10}-SO_2(C_{n'}H_{2n'+1})$, with $\mathbf{R^{10}}$ and $\mathbf{R^{10*}}$ are, independently from one another, a moiety selected in the group consisting of H and a C_{1-4} alkyl moiety ;

$\mathbf{R^{13}}$ is a moiety selected in the group consisting of H, $-C_{n'}H_{2n'+1}$, $-(CH_2)_nCO_2H$, $-CH(CH_2)_2$, $-(CH_2)_n-CO-C_{n'}H_{2n'+1}$, $-OH$, $-OCF_3$, $-OC_{n'}H_{2n'+1}$, $-O-(CH_2)_nCO_2H$, $-COH$, $-CO-C_{n'}H_{2n'+1}$, $-CO-(CH_2)_nCO_2H$, -O-benzoyl, $-SO_2H$, $-SO_2-C_{n'}H_{2n'+1}$, $-O-SO_2H$, $-O-SO_2-C_{n'}H_{2n'+1}$, $-NO_2$, $-NH_2$, $-NH(C_{n'}H_{2n'+1})$, $-N(C_{n'}H_{2n'+1})(C_{n'}H_{2n'+1})$, $-NH-CO-(C_{n'}H_{2n'+1})$, $-SH$, $-SC_{n'}H_{2n'+1}$, $-(CH_2)_n-N(R^{10})(R^{10*})$, $-(CH_2)_n-CO-N(R^{10})(R^{10*})$, $-O-SO_2-N(R^{10})(R^{10*})$, $-CO-SO_2-N(R^{10})(R^{10*})$, $-SO_2-N(R^{10})(R^{10*})$, $-NR^{10}-SO_2CF_3$, $-NR^{10}-SO_2(C_{n'}H_{2n'+1})$;

$\mathbf{R^5}$, $\mathbf{R^6}$ and $\mathbf{R^7}$ are, independently from one another, a moiety of the following general formula : $-(R^{11})_n-R^{12}$;

$\mathbf{R^{12}}$ is a moiety selected in the group consisting of -H, $-C_{n'}H_{2n'+1}$, $-N(C_{n'}H_{2n'+1})(C_{n'}H_{2n'+1})$, $-NO_2$, -Cl, -Br, -CN, -F, $-CF_3$,

$-OH$, $-(CH_2)_n-COOH$, $-C(OH)(CH_3)_2$, $-C(OH)(CF_3)_2$, $-SO_2CF_3$, $-SO_2(C_{n'}H_{2n'+1})$ and :



;

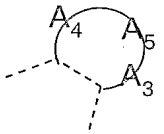
A_3, A_4 and A_5 are, independently from one another, an atom selected in the group consisting of C, N, O and S ;

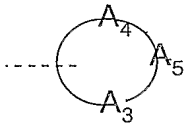
with in all the above :

n is, independently from one another, an integer ranging from 0 to 6,

n' is, independently from one another, an integer ranging from 1 to 8, preferably from 1 to 4, preferably from 1 to 3 and more preferably from 1 to 2.

According to special embodiments, the moiety :





is intended to designate :

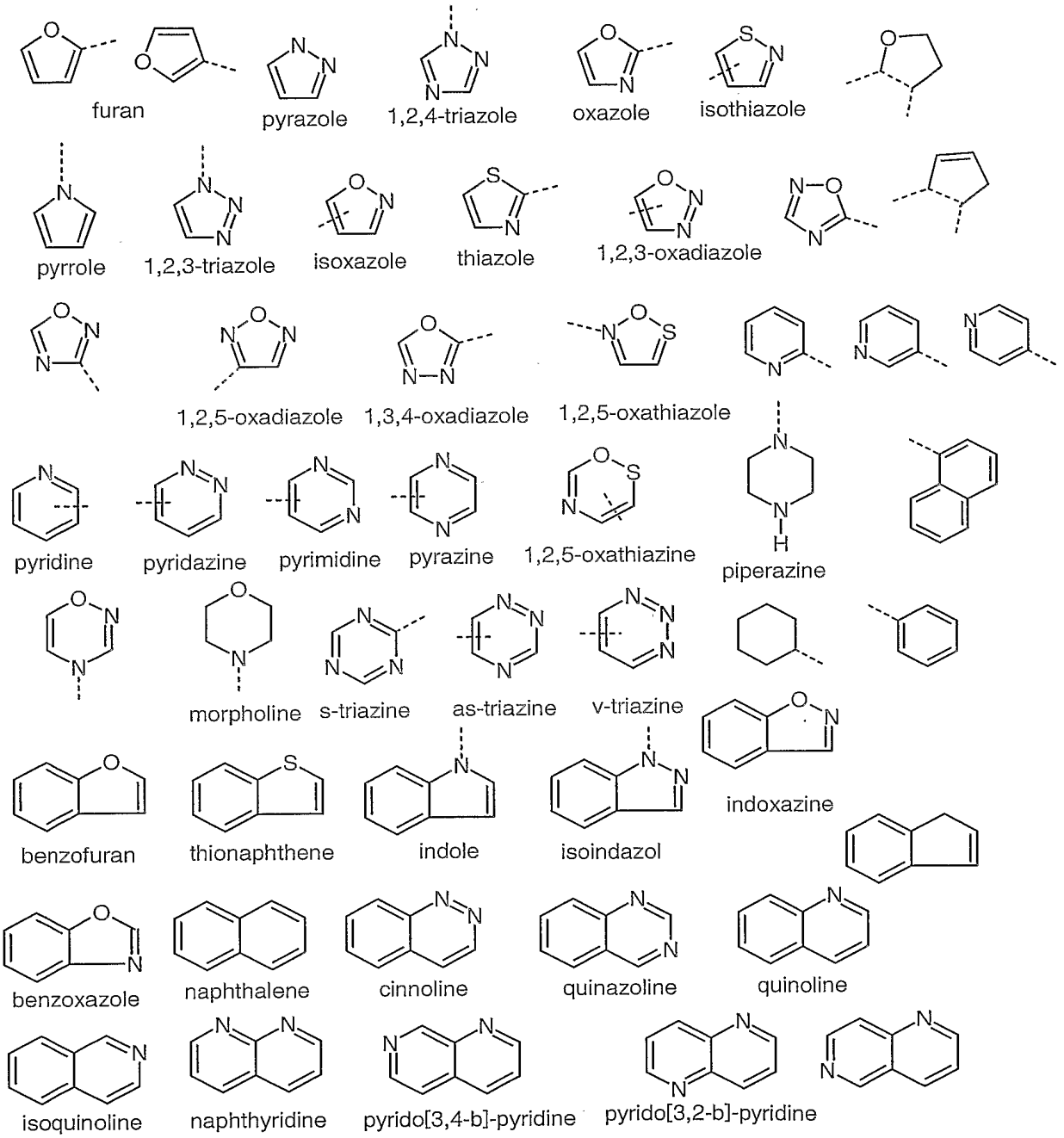
(i) a mono carbocyclic ring (i.e. a cyclic carboalkyl, with A_3, A_4 and A_5 are C)

(ii) a mono heterocyclic ring (i.e. a cyclic heteroalkyl, with at least one A_3, A_4 and/or A_5 is selected in the group consisting of N, S and O)

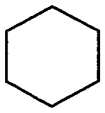
(iii) a bi- carbocyclic ring (i.e. a bicyclic carboalkyl with A_3, A_4 and A_5 are C)

(iv) a bi- heterocyclic ring (i.e. a bicyclic heteroalkyl with at least one cyclic ring is containing at least one A_3, A_4 and/or A_5 selected in the group consisting of N, S and O).

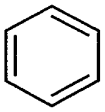
Additionally, said carbocyclic and/or heterocyclic ring (including both mono and bi) can be unsaturated, or partially or completely saturated, and is containing from 5 to 10 atoms. Examples of said carbocyclic and/or heterocyclic rings are :



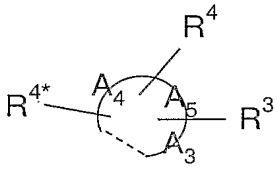
According to one special embodiment, the cycle designated with :

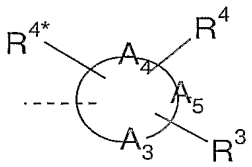


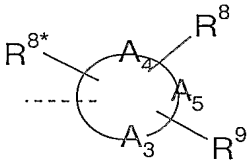
is under the form of an aromatic cycle :



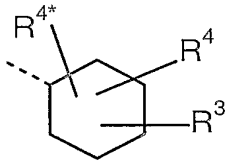
According to the present invention, the substituting moiety R present in the moiety :

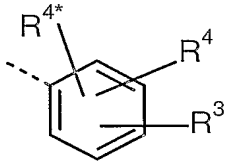






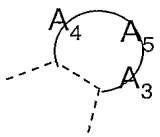
for example a cycle, such as for example the followings :



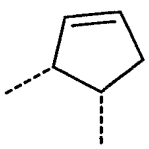


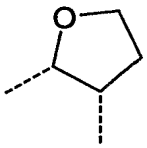
can be localized in position para, meta and/or ortho of said cycle. In preferred embodiment, the substituting moiety is localized in position para or meta.

According to one special embodiment, the cycle designated with :



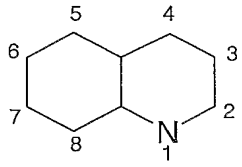
is selected in the group consisting in :





According to special embodiments, at least one moiety selected in the group R^5, R^6 and R^7 is a hydrogen-bound acceptor.

According to another special embodiment, at least one moiety selected in the group R^5, R^6 and R^7 is in position 6 or/and position 7 with :



According to another special embodiment, at least one moiety selected in the group R^5, R^6 and R^7 of the general formula $-(R^{11})_n-R^{12}$ is selected in the group consisting of $-CO-C_{n'}H_{2n'+1}$, $-O-C_{n'}H_{2n'+1}$, $-CO-O-C_{n'}H_{2n'+1}$, $-CO-CF_3$, $-O-CF_3$, $-C(OH)(CH_3)_2$, $-C(OH)(CF_3)_2$. In particular embodiments, it is containing at least one CF_3.

According to another special embodiment, the moiety R^3 and/or R^4 and/or R^8 and/or R^9 of compound of formula (I) is containing a cycloalkyl, said cycloalkyl being itself substituted with at least one moiety $\mathbf{R^{14}}$, with $\mathbf{R^{14}}$ is a moiety selected in the group consisting of H, -Cl, - CF_3, -F, -Br, -CN, $-C_{n'}H_{2n'+1}$, a cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety or a cycloheptyl), $-(CH_2)_nCO_2H$, $-CH(CH_2)_2$, $-(CH_2)_n-CO-C_{n'}H_{2n'+1}$, $-(CH_2)_n$-CO-cycloalkyl (e.g. $-(CH_2)_n$ -CO-cyclohexyl or $-(CH_2)_n$ -CO-phenyl), $-(CH_2)_n$-cycloalkyl (e.g. $-(CH_2)_n$-cyclohexyl or $-(CH_2)_n$-phenyl), -OH, $-OCF_3$, $-OC_{n'}H_{2n'+1}$, $-O-(CH_2)_n$- cycloalkyl (e.g. $-O-(CH_2)_n$-cyclohexyl or $-O-(CH_2)_n$-phenyl), $-O-(CH_2)_nCO_2H$, -COH, $-CO-C_{n'}H_{2n'+1}$, $-CO-(CH_2)_n$-cycloalkyl (e.g. $-CO-(CH_2)_n$-cyclohexyl or $-CO-(CH_2)_n$-phenyl), $-CO-(CH_2)_nCO_2H$, $-O-CO-(CH_2)_n$-cycloalkyl (e.g. -O-CO-

$(CH_2)_n$-cyclohexyl or -O-CO-$(CH_2)_n$-phenyl), -O-benzoyl, $-SO_2H$, $-SO_2-C_{n'}H_{2n'+1}$, $-SO_2-(CH_2)_n$- cycloalkyl (e.g. $-SO_2-(CH_2)_n$-cyclohexyl or $-SO_2-(CH_2)_n$-phenyl), $-SO_2-CO-(CH_2)_n$- cycloalkyl (e.g. $-SO_2-CO-(CH_2)_n$-cyclohexyl or $-SO_2-CO-(CH_2)_n$-phenyl), $-SO_2-CO-$(cycloalkyl (e.g. $-SO_2-CO-$cyclohexyl or $-SO_2-CO-$phenyl), $-O-SO_2H$, $-O-SO_2-C_{n'}H_{2n'+1}$, $-O-SO_2-(CH_2)_n$-cycloalkyl (e.g. $-O-SO_2-(CH_2)_n$-cyclohexyl or $-O-SO_2-(CH_2)_n$-phenyl), $-O-SO_2-CO-(CH_2)_n$- cycloalkyl (e.g. $-O-SO_2-CO-(CH_2)_n$-cyclohexyl or $-O-SO_2-CO-(CH_2)_n$-phenyl), $-O-SO_2-CO-$(cycloalkyl (e.g. $-O-SO_2-CO-$cyclohexyl or $-O-SO_2-CO-$phenyl), $-NO_2$, $-NH_2$, $-NH(C_{n'}H_{2n'+1})$, $-N(C_{n'}H_{2n'+1})(C_{n'}H_{2n'+1})$, $-NH-(CH_2)_n$- cycloalkyl (e.g. $-NH-(CH_2)_n$-cyclohexyl or $-NH-(CH_2)_n$-phenyl), $-NH-CO-(C_{n'}H_{2n'+1})$, $-NH-CO-(CH_2)_n$-cycloalkyl (e.g. $-NH-CO-(CH_2)_n$-cyclohexyl or $-NH-CO-(CH_2)_n$-phenyl), $-NH-CO-$cycloalkyl (e.g. $-NH-CO-$cyclohexyl or $-NH-CO-$phenyl), $-SH$, $-SC_{n'}H_{2n'+1}$, $-S-(CH_2)_n$-cycloalkyl (e.g. $-S-(CH_2)_n$-cyclohexyl or $-S-(CH_2)_n$-phenyl), $-S-CO-(CH_2)_n$- cycloalkyl (e.g. $-S-CO-(CH_2)_n$-cyclohexyl or $-S-CO-(CH_2)_n$-phenyl), $-S-CO-$(cycloalkyl (e.g. $-S-CO-$cyclohexyl or $-S-CO-$phenyl), $-(CH_2)_n-N(R^9)(R^{9*})$, $-(CH_2)_n-CO-N(R^9)(R^{9*})$, $-O-SO_2-N(R^9)(R^{9*})$, $-CO-SO_2-N(R^9)(R^{9*})$, $-SO_2-N(R^9)(R^{9*})$, $-NR^9-SO_2CF_3$, $-NR^9-SO_2(C_{n'}H_{2n'+1})$, with $\mathbf{R^9}$ and $\mathbf{R^{9*}}$ are, independently from one another, a moiety selected in the group consisting of H and a C_{1-4} alkyl moiety.

According to another special embodiment, the compound of the Invention is containing at least one -OH moiety is oxidized and said -OH moiety is thereby replaced by the =O moiety. Such a derivative of compound of formula (I) (or formula (II) below) is considered as a special embodiment of the present invention.

According to the present invention, the term "alkyl" as used herein, alone or in combination, is intended to designate a straight or branched chain, or cyclic carbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and

multi-moities. Typically, an alkyl moiety will have from 1 to 24 carbon atoms, with those moieties having 10 or fewer carbon atoms being preferred in the present invention. In rather preferred embodiment, the alkyl moieties of the invention are lower alkyl. A "lower alkyl" (e.g. $C_{n'}H_{2n'+1}$) is a shorter alkyl chain having eight or fewer carbon atoms (e.g. $n' \leq 8$), preferably six or fewer carbon atoms (e.g. $n' \leq 6$), and even more preferably 4 or fewer carbon atoms (i.e. C_{1-4}). Typically, a C_{1-4} alkyl moiety according to the invention will have from 1 to 2 carbon atoms, with those moieties having 1 carbon atom being preferred in the present invention. Examples of saturated alkyl moieties include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, (cyclohexyl)methyl, cyclopropylmethyl, n-pentyl, isopentyl, n-hexyl, isohexyl, n-heptyl, isoheptyl, n-octyl, and the like. An unsaturated alkyl moiety is one comprising one or more double bonds or triple bonds. Examples of unsaturated alkyl moieties include, but are not limited to, aromatic cycles such as phenyl and benzyl.

Additionally, the term "alkyl" is intended to further include those derivatives of alkyl comprising at least one heteroatom, selected from the group consisting of O, N and/or S (i.e. at least one carbon atom is replaced with one heteroatom). These alkyl derivatives are widely named "heteroalkyl" and as alkyl above described are intended to designate, by themselves or as part of another substituent, stable straight or branched chains, or cyclic moieties, or combinations thereof. According to specific embodiment, the nitrogen and sulfur atoms when present in the said heteroalkyl are further oxidized and/or the nitrogen heteroatom is quaternized. The heteroatom may be placed at any position of the heteroalkyl moiety, including the

position at which the alkyl moiety is attached to the remainder of the molecule.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or as part of another substituent, are intended to designate cyclic versions of the above "alkyl" and "heteroalkyl", respectively. They include bicyclic, tricyclic and polycyclic versions thereof.

It should be noted that the compounds of formula I (or above formula II) are comprising several moieties that can be repeated n times (e.g. $-O-(CH_2)_nCOOH$); it should be understood that each n value throughout the formula I (or formula II) in a particular compound can be chosen independently from one another. According to special embodiments of the invention, n is an integer ranging from 0 to 4, more particularly from 0 to 2, and even more particularly from 0 to 1. In a special case it is 0.

Similarly, the compounds of formula I (or above formula II) are comprising several moieties and/or atoms that can be present many times throughout one particular formula I (or formula II) (e.g. A_1-A_5, R^3, R^4, R^8, R^9...); it should be understood that each individual moieties and/or atoms throughout the formula I (or formula II) in a particular compound can be chosen independently from one another.

According to the present invention, the term C_{1-4} alkyl is intended to designate a straight or branched chain, which may be fully saturated, mono- or polyunsaturated, having from 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, iso-propyl, and the like. Typically, a C_{1-4} alkyl moiety according to the invention will have from 1 to 2 carbon atoms, with those moieties having 1 carbon atom being preferred in the present invention. An unsaturated alkyl moiety is one comprising one or more double bonds or triple bonds.

Examples of compounds according to the present invention are :

1-[4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanone,

4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX156651 or CRX000908 or CRX000909),

1-[4-(2-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanone,

4-(4-Nitro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-Naphthalen-1-yl-3a,4,5,9b-tetrahydro-3Hcyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanone,

4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

4-(2-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

4-(2,3-Dichloro-phenyl)-8-nitro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

8-Chloro-4-(2-chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(2,4-Dichloro-phenyl)-8-methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid methyl ester,

4-(4-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

4-(2-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid ethyl ester,
4-(4-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid ethyl ester,
4-(3-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,
4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid,
4-(4-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid,
4-(3-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid,
4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid,
4-(2-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid,
4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid,
4-(4-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid,
4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid diethylamide,
4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid diethylamide,
4-(4-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid diethylamide,
[4-(4-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-6-yl]-morpholin-4-yl-methanone,
4-Furan-2-yl-8-methoxy-2,3,3a,4,5,9b-hexahydro-furo[3,2c]quinoline,
4-Phenyl-2,3,3a,4,5,9b-hexahydro-furo[3,2c]quinoline,
4-(2-Methoxy-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(2-Chloro-4-fluoro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline ,

4-(2-Nitro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-Biphenyl-4-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(2-Chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(4-Chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(3-Fluoro-2-methyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(2-Ethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(2,3-Dimethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

8-Trifluoromethoxy-4-(2-trifluoromethyl-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(2-Fluoro-3-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

[3-Chloro-4-(8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenyl]-dimethyl-amine,

4-(2-Chloro-3-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

2-(8-Trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-phenylamine,

4-(2-Chloro-4-fluoro-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline,

4-Biphenyl-4-yl-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline,

4-(2-Methoxy-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline,

4-(2-Chloro-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline,

4-(4-Chloro-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline,

4-(2,3-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000292)

4-Phenyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000293)

1-[4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl]-2,2,2-trifluoro-ethanone (CRX 000295)

4-Furan-2-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000319)

2-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol (CRX 000321)

2-[4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol (CRX 000322)

4-(2,3-Dichloro-phenyl)-8-methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000361)

4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-ol (CRX 000368)

4-(2,4-Dichloro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000369 or CRX001045 or CRX001046)

4-(2,3-Dichloro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000370)

4-(2,4-Dichloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000374)

1-(4-Furan-2-yl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)-ethanone (CRX 000387)

4-Thiophen-2-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000406)

4-(2,6-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000409)

4-Naphthalen-1-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000412)

4-Benzyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline(CRX 000413)

4-Cyclohexyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000415)

5-Benzyl-4-(2,4-dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000416)

4-Thiophen-3-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000429)

4-Thiazol-2-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000430)

4-Pyridin-4-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000507)

4-(5-Phenyl-thiophen-2-yl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000508)

4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester (CRX 000525)

4-Phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester (CRX 123505)

4-(2-Methoxy-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline(CRX 000558)

4-(2-Chloro-4-fluoro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000564)

4-(2-Nitro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000567)

4-Biphenyl-4-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000568)

4-(2-Chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000569)

4-(4-Chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000570)

4-(3-Fluoro-2-methyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000593)

4-(2-Ethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000595)

4-(2,3-Dimethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000596)

8-Trifluoromethoxy-4-(2-trifluoromethyl-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000612)

4-(2-Fluoro-3-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000613)

[3-Chloro-4-(8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenyl]-dimethyl-amine (CRX000614)

4-(2-Chloro-3-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000646)

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000320)

4-(3-Nitro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000323)

4-Methyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000408)

4-tert-Butyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000410)

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid ethyl ester(CRX000414)

4-(4-Fluoro-2-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000740)

8-Trifluoromethoxy-4-(4-trifluoromethoxy-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000741)

4-(4-Ethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000742)

3-Chloro-4-(8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenol (CRX 000743)

4-(2,4-Bis-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000744)

4-(2-Fluoro-4-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000745)

4-(3,5-Dichloro-pyridin-4-yl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000763)

4-(3,4-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000764)

4-Cyclopropyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000863)

4-Piperidin-4-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000899)

4-(2-Chloro-4-methoxy-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000903)

4-(8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-piperidine-1-carboxylic acid tert-butyl ester (CRX 000905)

4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000737)

4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-ol (CRX 000738)

4-(2,4-Dichloro-phenyl)-8-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000739)

4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carbonitrile (CRX 000746)

[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-acetic acid (CRX 000747)

[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-dimethyl-amine (CRX 000794)

[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-methanol (CRX 000896)

4-Cyclohexyl-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000977)

4-(4-Fluoro-2-trifluoromethyl-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000997)

4-(2-Nitro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001000)

6-Chloro-4-(2,4-dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001066)

N-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-methanesulfonamide (CRX 001018)

1,1,1,3,3,3-Hexafluoro-2-(3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)-propan-2-ol (CRX 000971)

1,1,1,3,3,3-Hexafluoro-2-[4-(4-fluoro-2-trifluoromethyl-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-propan-2-ol (CRX 000860)

2-(4-Cyclohexyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)-1,1,1,3,3,3-hexafluoro-propan-2-ol(CRX 000861)

4-(2,4-Dichloro-phenyl)-7-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000792)

4-(2,4-Bis-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000969)

6-Chloro-4-(2,4-dichloro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001083)

7-Chloro-4-(2,4-dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001084)

6-Chloro-4-(4-fluoro-2-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001087)

6-Chloro-4-phenyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001088)

6-Chloro-4-cyclohexyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001113)

4-(2,4-Dichloro-phenyl)-8-isopropyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001114)

1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-2,2,2-trifluoro-ethanone (CRX001085)

4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid amide (CRX 000760)

4-(2,4-dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-ylamine (CRX 000765)

2-[4-(2,4-Dichloro-phenyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol (CRX000927)

2,2,2-Trifluoro-1-(8-trifluoromethoxy-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]quinolin-5-yl)-ethanone (CRX000953)

8-Trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline (CRX000961)

1,1,1,3,3,3-Hexafluoro-2-[4-(4-fluoro-2-trifluoromethyl-phenyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-8-yl]-propan-2-ol (CRX000966)

4-Cyclohexyl-8-trifluoromethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline (CRX000990)

4-(4-Fluoro-2-trifluoromethyl-phenyl)-8-trifluoromethyl-2,3,3a,4,5,9b-hexahydro-4-Trifluoromethyl-phenylamine 1H-cyclopenta[c]quinoline (CRX001016)

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid (CRX000762)

4-Furan-2-yl-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline (CRX000385)

8-Methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline-4-carboxylic acid ethyl ester (CRX000489)

4-Furan-2-yl-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline (CRX000488)

[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-methanol (CRX000896)

1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanol (CRX000906)

1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-2,2,2-trifluoro-ethanol (CRX001116)

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid 2,4-dichloro-benzylamide

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid 4-chloro-benzylamide

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid [2-(4-chloro-phenyl)-ethyl]-amide

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid (2-ethyl-phenyl)-amide

[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yloxy]-acetic acid

2-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yloxy]-2-methyl-propionic acid

2-[3-Chloro-4-(8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenoxy]-2-methyl-propionic acid

[3-Chloro-4-(8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenoxy]-acetic acid

4-(4-Benzyloxy-2-chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

4-(4-Fluoro-2-trifluoromethyl-phenyl)-8-(2,2,2-trifluoro-1-methoxy-1-trifluoromethyl-ethyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

1-[4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]quinolin-5-yl]-2,2,2-trifluoro-ethanone

4-(2,4-Dichloro-phenyl)-5-methyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

2,2,2-Trifluoro-1-(8-trifluoromethoxy-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl)-ethanone

5-Benzenesulfonyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

5-(2,4-Dichloro-benzyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

2-[5-(2,4-Dichloro-benzyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol

2,2,2-Trifluoro-1-[8-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl]-ethanone

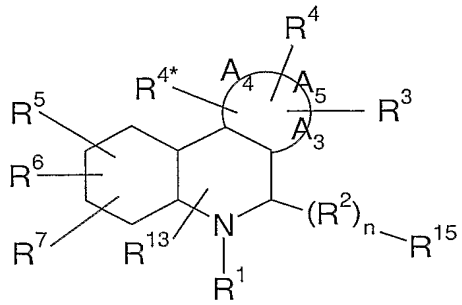
5-Methyl-8-(2,2,2-trifluoro-1-methoxy-1-trifluoromethyl-ethyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

1-[4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl]-propan-1-one.

Advantageously, the compound of the invention is selected among the group consisting in (i) 4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX156651 or the pure enatiomer CRX000908 or CRX000909, particularly CRX000908), and (ii)4-

(2,4-Dichloro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000369 or the pure enatiomer CRX001045 or CRX001046); or (iii) analogues, derivatives, solvates or salts thereof.

According to a second embodiment, the present invention concerns compounds of the general formula (II):



or analogues, derivatives, solvates or salts thereof,

wherein :

R^{15} is a moiety selected in the group consisting of -H, $-C_{n'}H_{2n'+1}$, $-N(C_{n'}H_{2n'+1})(C_{n'}H_{2n'+1})$, $-NO_2$, -Cl, $-CF_3$, -OH, $-(CH_2)_n$-COOH, $-SO_2CF_3$, phenyl, $-(CH_2)_n$-phenyl, and $-SO_2(C_{n'}H_{2n'+1})$;

and all other moieties and numbers are as above described in general formula (I).

The terms "analogues, derivatives, solvates or salts of compounds of the present invention" include both the structural derivatives and analogues of said compounds, their pharmaceutically acceptable solvates or salts, their stereoisomers, esters, prodrug forms, or their polymorphs. All these type of compounds are herein designated by the generic term "compounds".

Those skilled in the art will recognize that the compounds of the present invention may be utilized in the form of a pharmaceutically acceptable salt thereof. The physiologically acceptable salts of the compounds of Formula (I) and/or (II) include conventional salts prepared with

pharmaceutically acceptable acids or bases, depending on the particular substituents found on the compounds described herein for dosing in mammals, especially humans. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, formic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, perchloric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from organic acids like acetic, lactic, propionic, isobutyric, palmoic, maleic, glutamic, hydroxymaleic, malonic, benzoic, succinic, glycolic, suberic, fumaric, mandelic, phthalic, salicylic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, hydroxynaphthoic, hydroiodic, and the like. Other acids such as oxalic, while not considered as pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, lithium, calcium, aluminium, ammonium, barium, zinc, organic amino, or magnesium salt, N,N^1-dibenzylethylenediamine, choline, diethanolamine, ethylenediamine, N-methylglucamine, procaine salts (e.g. chloroprocaine) and the like. Also included are salts of amino acids such as arginate and the

like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 66, 1-19). Finally, certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Similarly, those skilled in the art will recognize that the compounds of the present invention may be utilized in the form of a pharmaceutically acceptable solvate thereof. These solvates may be prepared by conventional methods such as dissolving the compounds of formula (I) and/or (II) in solvents such as methanol, ethanol and the like.

References hereinafter to a compound according to the invention include both compounds of Formula (I) and/or (II) and their pharmaceutically acceptable salts and solvates.

Additionally, those skilled in the art will recognize that stereocenters exist in compounds of Formula (I) and/or (II). Accordingly, the present invention includes all possible stereoisomers including optical and geometric isomers of Formula (I) and/or (II). It further includes not only racemic compounds, or racemic mixtures thereof, but also the optically active isomers as well. When a compound of Formula (I) and/or (II) is desired as a single enantiomer, it may be obtained either by resolution of the final product or by a stereospecific synthesis from either optically pure starting material or any convenient intermediate. Additionally, in situations where tautomers of the compounds of Formula (I) and/or (II) are possible, the present invention is intended to include all tautomeric forms of the compounds. These terms and methods required for identifying and selecting the desired compounds are well known in the art. For example, diastereoisomers may be separated by

physical separation methods such as fractional crystallization and chromatographic techniques, and enantiomers may be separated from each other by the selective crystallization of the diastereomeric salts with optically active acids or bases or by chiral chromatography (see experimental section). Pure stereoisomers may also be prepared synthetically from the appropriate stereochemically pure starting materials, or by using stereoselective reactions. According to special embodiments, the relative stereochemistry of the compounds of the Invention is SYN.

According to a particular embodiment, the active compound of the Invention is an enantiomer selected in the group consisting of compounds CRX000908, CRX001075, CRX001046 and CRX001072.

In special embodiments, e.g in the case of the -COOH being present, the compounds of the present invention might be in a prodrug form. A prodrug is in most cases a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. Therefore, prodrugs of a compound of general formula (I) and/or (II) is a compound which has chemically or metabolically cleavable groups and which readily undergoes chemical changes under physiological conditions to provide a compound of formula (I) and/or (II) *in vivo*. Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, alkyl esters prepared by reaction of the parent acid compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Particularly preferred alkyl esters as prodrugs are formed from methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido. Methyl ester

prodrugs, for example, may be prepared by reaction of the acid form of a compound of general formula (I) in a medium such as methanol with an acid or base esterification catalyst (e.g., NaOH, H_2SO_4). Ethyl ester prodrugs are prepared in similar fashion using ethanol in place of methanol. Details regarding prodrugs are available for example in US 5,498,729.

Those skilled in the art are further able to prepare various polymorphs of a compound of general formula (I) and/or (II) for example by crystallization of compound of formula (I) and/or (II) under different conditions. For example, he can use different solvents or mixtures commonly used for crystallization. Similarly, he can crystallize compounds of general formula (I) and/or (II) at different temperatures, according to various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

According to special embodiments, the compounds of the invention may be labeled in a variety of ways. For example, the compounds may contain radioactive isotopes such as, for example H^3 (tritium) or C^{14} at one or more of the atoms that constitute compounds of general formula (I) and/or (II). Similarly, the compounds may be advantageously joined directly, covalently or noncovalently, or through a linker molecule, to a wide variety of other moieties, which may provide function as carriers, labels, adjuvents, coactivators, stabilizers, etc. Such labeled and joined compounds are contemplated within the present invention.

The invention further concerns composition comprising at least one compound of the general formula (I) and/or (II) as above disclosed.

The compounds and compositions of the present invention are further characterized by their properties towards nuclear receptor LXRs. More specifically, representative compounds and compositions of the Invention were demonstrated to have pharmacological activity in *in vitro* and *in vivo* assays, e.g., they are capable of specifically modulating a cellular physiological response to reduce an associated pathology or provide or enhance a prophylaxis. More specifically, the Applicant has shown that the compounds of general formula (I) and/or (II) are first able to interact with at least one LXR receptor, more specifically with LXR-alpha or LXR-beta; they are thus named LXR, LXR-alpha or LXR-beta ligands, respectively. More preferred compounds are those, which are able to interact at least with the ligand binding domain (LBD) of at least one LXR receptor, more specifically with the LBD of LXR-alpha (i.e. amino acids 164-447 for human LXR-alpha (reference : DNA sequence U22662 ; Protein id AAA85856.1), and/or amino acids 155-461 for human LXR-beta (reference : DNA sequence U07132, Protein id AAA61783.1). The distinction between binding to the LXR-alpha or LXR-beta can be routinely examined according to well known method (e.g. see below and the Experimental Section). In even more specific embodiments, the compounds and compositions of the invention are those which bind to the LBD of at least one LXR receptor, more specifically with the LBD of LXR-alpha or of LXR-beta, with (i) a constant of dissociation (Ki) comprised in the range of about 25 nM to about 3000 nM, with preference for Ki of less than about 3uM and more than about 25nM, with more preferred embodiment in the range of about 25nM to about 500nM and even more preferred of about 25nM to about 250nM and/or with (ii) an affinity of less than about 1uM and more

than about 1nM, with concentrations in the range of about 10 to about 500nM being preferred. In preferred embodiments, the compounds or compositions of the Invention are those which bind to the LBD of LXR-alpha (i.e. LXR-alpha ligands).

It should be noted that as mentioned above, in special embodiments, the compounds of the Invention can include racemic compounds, racemic mixtures thereof, or optically active isomers. Accordingly the said measured affinity can vary for one special compound of the Invention depending on its racemic status. According to even more specific embodiments, the compounds and compositions of the invention are those which under their form of racemate are binding to the LBD of at least one LXR receptor, more specifically with the LBD of LXR-alpha, with an affinity of less than about 1uM and more than about 1nM, and which under the dextrogyre or levogyre form have an affinity of less than about 500nM, more specifically less than about 250nM.

Methods and conditions for testing or measuring the interacting and/or binding property of compounds (i.e. ligands) with nuclear receptors and/or LBD are widely disclosed and implemented in the art : for examples, Glickman et al., 2002, J. Biomolecular Screening, 7, 3-10 or Lehmann et al., 1995, J. Biol. Chem., 270, 12953-12956. For example, Le Douarin et al., (2001, Methods Mol. Biol., 176, 227-48) have disclosed an *in vitro* screening test using the yeast two-hybrid system that is based on the ligand-dependent interaction of two proteins, a hormone receptor and a coactivator ; Zhou et al., (2001, Methods, 25, 54-61) have disclosed a homogeneous time-resolved fluorescence (HTRF) energy transfer technology which is sensitive, homogeneous, and nonradioactive ; Beaudet et al., (2001,Genome Res., 11, 600-8) have disclosed the AlphaScreen™ technology (Packard BioScience) which allows the development of high-throughput homogeneous proximity assays. The full content of these

papers is incorporated herein by reference. Specific examples of said standard procedures available in the art are the Fluorescence Resonance Energy Transfer (FRET), the CoActivator-dependent Receptor Ligand Assay (CARLA) and the GST-pull down assays or two-hybrid assays (see Experimental Section).

According to another embodiment, the compounds of the present invention modulate the transcriptional activity of LXRs (i.e. they are useful for modulating LXRs functions). "Modulate the transcriptional activity of LXRs" means that the compounds of the present invention are able to effect transcriptional activation and/or to inhibit or silence transcription of genes which are transcriptionally modulated (i.e. activated and/or inhibited or silenced) by the said nuclear receptors and thus the biological and/or pharmacological effects mediated by these nuclear receptors. In particular embodiments, the compounds and compositions of the present invention are able to modulate the transcriptional activity of either LXR-alpha or LXR-beta, i.e. they are useful for modulating either LXR-alpha or LXR-beta function, and thus the biological/pharmacological responses mediated by said nuclear receptors, respectively.

Ability of compounds and compositions of the invention to specifically modulate the LXRs functions, more preferably LXR-alpha functions, may be first evaluated *in vitro* for their ability to modulate LXR receptors biological effects using biochemical assays (see, for example, the assays above mentioned; e.g. AlphaScreen™ technology) or in cell-based assays. For example, a system for reconstituting ligand-dependent transcriptional control has been developed by Evans et al., 1988, Science, 240, 889-95 and has been termed "co-transfection" or "cis-trans" assay. This assay is described in more detail in US 4,981,784 and US 5,071,773, which are incorporated herein by reference. Also see Heyman et al.,

1992, Cell, 68, 397-406, Kliewer et al., 1995, Cell 83, 813-819 , Lehmann et al., 1995, J. Biol. Chem., 270, 12953-12956, or Lehnman et al. 1997, J. Biol. Chem., 272, 3137-3140. The co-transfection assay provides a method to evaluate the ability of a compound to modulate the transcriptional response initiated by a nuclear receptor, for example LXRs. The co-transfection assay is a functional, rapid assay that monitors hormone or ligand activity, is a good predictor of the *in vivo* activity, and can be used to quantitate the pharmacological potency and utility of such ligands in treating various disease states (Berger et al., 1992, J. Steroid Biochem Molec. Biol., 41, 733-38). Briefly, the co-transfection assay involves the introduction of various plasmids by transient transfection into a mammalian cell : at least a plasmid which contains a nuclear receptor receptor cDNA (e.g. LXR-alpha or LXR-beta) and directs constitutive expression of the encoded receptor ; and at least a plasmid which contains a cDNA that encodes for a readily quantifiable protein, e.g., firefly luciferase, chloramphenicol acetyl transferase (CAT), or alkaline phosphatase (SPAP or SEAP), under control of a promoter containing at least one LXR response element, which confers LXR dependence on the transcription of the reporter gene. This assay can be used to accurately measure efficacy and potency of interaction and modulating activity of a reference ligand compound or of a tested compound. Actually, when added to the assay, if the reference or tested compound binds to the nuclear receptor, the later undergoes a conformation change that promotes or inhibits transcription of the reporter genes.

Alternatively, Voegel et al. (1998, EMBO J. 17, 507-519) have proposed the use of transient transfection assays with a GAL4 reporter plasmid and chimeras containing various peptide fragments (i.e. putative or identified LBD of LXRs or LXR-alpha/beta) fused to the GAL4 DBD (DNA Binding Domain). The

resultant construct is introduced into cells (e.g. HEK293, yeast,...) together with UAS-containing reporter construct (e.g. luciferase). The co-transfected cells are then treated with chemical compounds and reporter activity is measured. Individual compounds are evaluated relative to a control (e.g. without compound) and the EC_{50} is determined as the concentration necessary to produce 50% of the maximal reporter activity observed with a reference ligand compound previously identified and used in the art.

It is further possible to analyze the modulating properties (i.e. their ability to increase or decrease LXRs targeted gene expression) of the compounds and compositions of the present Invention using western-blot analysis, northern-blot analysis (see Experimental Section) or *in vivo*, in established cell lines or animal models. These methods are widely used in the field by the one skilled in the art. Particularly, it is possible to analyze target gene expression in hepatocytes, macrophages and colon cells. Examples of adapted cell models are HepG2 (liver - ATCC HB-8065), THP-1 (macrophage - ATCC TIB-202), Caco-2 or HT-29 (Intestine - ATCC HTB-37 and ATCC HTB-38, respectively). The modulator effect of the compounds and compositions of the Invention on the expression of LXRs target genes can be tested in animal model, such as for example mice strain C57/BL6 (Schultz - *infra*) or hamster or rabbit. According to preferred embodiment, the examined target gene are selected in the group consisting of LXRs target gene encoding products implicated in lipogenesis (e.g. FAS, SREBP1c, SCD-1, ACC), cholesterol efflux (e.g. ABCA1), hypertriglyceridemia (e.g. Angptl3) and/or glucose metabolism (PEPCK). The animal models which are particularly useful to evaluate cholesterolemic effects of the compounds and compositions of the present invention are well known in the art. For example, compounds and compositions disclosed herein can lower cholesterol

levels in hamsters fed a high-cholesterol diet, using a protocol similar to that described in Spady et al. (1988, J. Clin. Invest., 81, 300), Evans et al. (1994, J. Lipid Res., 35, 1634), or Lin et al (1995, J. Med. Chem., 38, 277). Still further, LXR-alpha animal models (e.g., LXR-alpha (+/-) and (-/-) mice) can be used for evaluation of the present compounds and compositions (see, for example, Peet, et al. 1998, Cell, 93, 693-704).

The modulating property of the compounds and compositions of the present invention towards LXRs (including LXR-alpha or LXR-beta) can be characterized in a cell-based assay or a peptide-sensor assay as presented above and are defined by their ability to improve, mimic, compete or block the effects of a LXRs full agonist or reference molecule, such as the naturally occurring sterols 24(S), 25-epoxycholesterol and 24(S)-hydroxycholesterol, or synthetic reference LXR full agonist e.g. T0901317 (Tularik), F3MethylAA (Merck) or GW3965 (Glaxo SmithKline).

According to one embodiment, the compounds and compositions of the present invention are LXRs and/or LXRs LBD agonists. According to another embodiment, the compounds and compositions of the present invention are specific agonist towards LXR-alpha and/or LXR-alpha LBD. According to another embodiment, the compounds and compositions of the present invention are specific agonist towards LXR-beta and/or LXR-beta LBD. By "agonist " is meant a compound or composition which when combined with an intracellular receptor stimulates or increases a reaction typical for the receptor, e.g., transcription activation activity. In one embodiment, said agonist is a LXR-alpha agonist, i.e. a LXR ligand which potentiates, stimulates, induces or otherwise enhances the transcriptional activity of a LXR-alpha receptor, e.g., such as by mimicking a natural physiological ligand for the receptor. In another embodiment, said agonist

is a LXR-beta agonist, i.e. a LXR ligand which potentiates, stimulates, induces or otherwise enhances the transcriptional activity of a LXR-beta receptor, e.g., such as by mimicking a natural physiological ligand for the receptor. A drug that produces at least the possible maximal effect (i.e. the maximal effect produced by a full agonist such as for example the above cited reference molecules) is called "full agonist". According to another embodiment, the compounds and compositions of the present invention are LXRs and/or LXRs LBD full agonists, and more particularly LXR-alpha and/or LXR-alpha LBD full agonists and/or LXR-beta and/or LXR-beta LBD full agonists. According to special embodiments, the compounds and compositions of the present invention are full agonists in the sense that their maximal efficacy (illustrated by their Vmax and/or Emax) is at least about 100% of the maximal efficacy (illustrated by Vmax and/or Emax) of the reference T0901317 (Tularik) or GW3965 (Glaxo SmithKline) measured under identical conditions (see the Experimental section). In special embodiments, their maximal efficacy is comprised between about 100% and about 120% of the T0901317 (Tularik) and/or GW3965 (Glaxo SmithKline) maximal efficacy.

According to another embodiment, the compounds and compositions of the present invention are LXRs and/or LXRs LBD partial-agonists. According to another embodiment, the compounds and compositions of the present invention are LXR-alpha and/or LXR-alpha LBD partial-agonists, and/or LXR-beta and/or LXR-beta LBD partial-agonists. A drug that produces less than the possible maximal effect (i.e. the maximal effect produced by a full agonist, or reference molecule) is called "partial agonist".

For example, the partial agonist property of the compounds and compositions of the present invention can be defined by reference to T0901317 (Tularik) which is a full

LXR agonist. Alternatively, it is possible to use other full LXR agonist such as the F3MethylAA (Merck) or GW3965 (Glaxo SmithKline) as reference molecules. According to special embodiments, the compounds and compositions of the present invention are partial agonists in the sense that their maximal efficacy (illustrated by their Vmax and/or Emax) is less than about 70%, preferably less than about 50%, of the maximal efficacy (illustrated by Vmax and/or Emax) of the T0901317 or GW3965 measured under identical conditions (see the Experimental section). In special embodiments, their maximal efficacy is comprised between about 70% and about 5% of the T0901317 or GW3965 maximal efficacy; in more special embodiments it is comprised between about 60% and about 10% of the T0901317 or GW3965 maximal efficacy; and in even more special embodiments it is comprised between about 30% and about 20% of the T0901317 or GW3965 maximal efficacy.

Potency and efficacy are the two key features in analyzing ligand agonist, including partial agonist, property. Potency can be calculated through dose response experiment in a given functional assay e.g. co-transfection assay (see above). It represents the dose of compound necessary to achieve 50 % of maximal effect (EC50). This value is closely related to the Kd obtained in a binding assay and therefore related to the affinity of the compound for the receptor. Identification of compounds with low potency is important to achieve target specificity and the development of low dosed pharmaceutical compositions to be administered to patients. Efficacy determines the maximum effect that can be achieved in a functional assay that assesses the compound tested effect on the LXRs, and more particularly LXR-alpha and/or LXR-beta, in a co-transfection assay. The Applicants postulate that too high level of efficacy can be associated with detrimental undesirable side effects. Thus, they proposed to seek for potent LXRs

ligands, especially LXR-alpha and/or LXR-beta ligands, with reduced efficacy (compared to T0901317 or GW3965 for example) which should result in safer drugs.

According to special embodiments, the compounds and compositions of the present invention have a potency (EC50) less than about 10uM, preferably less than about 1uM. More specifically, it is comprised between about 2uM and about 1nM, with concentrations in the range of about 10 to about 500nM being preferred.

As mentioned above, when the compound of the Invention exists under a racemate mixture form, the potency (EC50) measured with the racemate can differ from the EC50 measured with the purified enantiomer (dextrogyre or levogyre).

According to another embodiment, the compounds of the present invention are selective of LXRs, and more specifically of LXR alpha. This means in particular that the said compounds are not binding with high affinity and/or potency with other nuclear receptors. This further means that the compounds and compositions of the present invention are not able to modulate function of other nuclear receptors.

According to one embodiment, the compounds and compositions of the present invention are binding with PXR and/or FXR with an EC50 superior to about 10 µM.

According to one embodiment, the compounds and compositions of the present invention are not able to modulate PPARs function, and more specifically PPAR-beta and/or PPAR-gamma and/or PPAR-alpha functions. These PPAR modulating activities may be measured by assays widely known to one skilled in the art such as for example those which are disclosed in WO0200611.

One of the major drawbacks of the previously developed LXRs modulators was illustrated by their LXRs target gene

activation profiles. More specifically, the known LXRs agonists (e.g. the reference molecules presented above) are able to activate genes involved both in cholesterol trafficking (e.g. ATP-binding cassette transporters A1 (ABCA1), G1 (ABCG1), G5 (ABCG5) and G8 (ABCG8), ApoE, LPL, PLTP, CETP), hypertriglyceridemia (e.g. Angptl3) and lipogenesis (e.g. FAS, SREBP1c / SREPB1a, SCD-1, ACC). Said expression profile leads *in vivo* to beneficial effects (i.e. increasing HDL-c, increasing RCT) but also to adverse effects (e.g. strong increase in plasma and/or liver triglycerides TG levels). The Applicants have now shown that it is possible to separate the two types of expression profiles (i.e expression of LXRs target genes involved in cholesterol efflux and of LXRs target genes involved in lipogenesis including hypertriglyceridemia) for a unique compound. More particularly, they have developed LXRs agonists, including partial agonists, that present low adverse LXRs activation of lipogenic genes while maintaining the beneficial LXRs activation of genes implicated in RCT promoting. Thus, according to one embodiment, the compounds and compositions of the present Invention have the ability to increase the expression of at least one LXRs target gene involved in cholesterol trafficking. In preferred embodiment, said LXRs target gene involved in cholesterol trafficking is selected in the group consisting of ATP-binding cassette transporters A1 (ABCA1), G1 (ABCG1), G5 (ABCG5), G8 (ABCG8), ApoE, LPL, PLTP and CETP. According to one special embodiment, said compounds and compositions are able to increase the expression of said gene in at least one tissue selected from the group consisting of liver, macrophage and intestine, and the like (e.g. isolated cells such as HepG2, THP-1, Caco-2 or HT-29). According to a more specific embodiment, the compounds and compositions of the Invention are able to induce the expression of the ABCA1 gene in cell model (e.g.

THP-1) to a level comparable to the one observed under the same conditions with a reference compound, e.g. GW3965. "Level comparable" means that the induction of the compound or composition under identical conditions is about identical, i.e. is about 70%, preferably about 80%, even preferably about 90%, advantageously 100% or more of the induction level observed under the same conditions with the reference compound.

In advantageous embodiments, the compounds and compositions of the present Invention have the ability to increase the expression of at least one LXRs target genes involved in cholesterol trafficking as above described and have a limited ability to increase the expression of at least one LXRs target genes involved in lipogenesis, including hypertriglyceridemia. In preferred embodiment, said LXRs target genes involved in lipogenesis are selected from the group consisting of FAS, SREBP1c, SCD-1, Angptl3 and ACC. In specific embodiment, said "limited ability" is measured in at least one tissue selected from the group consisting of liver, adipose tissue, macrophage, intestine, and the like (e.g. isolated cells such as HepG2, THP-1, Caco-2 3T3-L1 or HT-29). According to one special embodiment, said compounds and compositions are able to increase the expression of ABCA-1 and have a limited ability to increase the expression of FAS and/or SREBP1c and/or Angptl3. According to the present invention, "limited ability" means that the compounds and compositions of the Invention induce the expression of the gene involved in lipogenesis (e.g. FAS and/or SREBP1c and/or Angptl3) in a cell model (e.g. HepG2) to a level that is greatly reduced compared to the one observed in the same conditions with a reference compound, e.g. GW3965 or T0901317. "Greatly reduced" means that the induction with the compound or composition under identical conditions is less than at least 70%, preferably less than about 50%, even

preferably less than about 40 %, advantageously less than about 30% and more advantageously less than about 20% of the induction level observed under the same conditions with the reference compound. For example, the reference compound T0901317 exhibits the following increase of the expression of FAS (about 87%) and/or Angptl3 (about 79%) and ABCA1 (about 69%) (see Experiments Section).

Alternatively, said "increase of the expression of at least one LXRs target genes" by the compounds and compositions of the present Invention is actually the illustration of the decrease or remove of an inhibition of said expression, said decrease or remove resulting from the action of the said compounds and compositions.

The measurement of the expression of at least one LXRs target genes can be performed by methods well known in the art, such as for example mRNA levels determination by RNAse protection assay (RPA) (Hylemon et al., 1992, J. Biol. Chem., 267, 16866-16871).

The compounds and compositions of the invention are further characterized by their biological/pharmacological activities, and more specifically present beneficial activities towards cholesterol metabolism by lowering, or at least by preventing increase of, one or more of the following biological entities in a patient: triglycerides, fatty acids, total cholesterol, LDL-c, VLDL-c, bile acid and the like. According to another embodiment, the compounds and compositions of the Invention are further characterized by their biological/pharmacological activities towards HDL-c by increasing its plasma level. In further embodiments, the compounds and compositions of the invention are characterized by their biological/pharmacological activities towards HDL-c and TG by increasing the HDL-c plasma level without increasing the TG plasma level and/or TG liver level. These

activities can be appreciated using methods widely used in the art and routinely implemented in laboratories. More specifically, these activities are appreciated with reference to any reference molecule which has already been identified in the art, such as T0901317 and/or GW3965.

According to another embodiment, the compounds or compositions of the Invention have the property to promote cholesterol efflux and/or enhance the Reverse Cholesterol Transport (RCT). These properties can be analyzed according to the methods disclosed in the Experimental Section.

According to another embodiment, the compounds and compositions of the present invention, when administered to a patient, do not lead to adverse effects, or are associated with reduced adverse effects, and more specifically do not lead or are not associated with liver adverse effects (e.g. hepatomegaly) or with peroxisome proliferation. These adverse effects are examined for example by measuring liver enzymes (ALT, AST, Alkaline phosphatase), plasma glucose, plasma free fatty acids, plasma insulin, body weight, liver weight, kidney weight,etc...

The compounds and compositions of the invention are further characterized by their biological/pharmacological activities towards atherosclerosis by lowering in a treated patient (including animal models such as LDLR-/- and ApoE-/- mice or in old obese monkey) the atherosclerosis plaque (i.e. the compounds and compositions of the invention have anti-atherosclerotic effects). Methods for measurement of atherosclerosis are available, e.g. angiographic methods, noninvasive ultrasound based methods (e.g. Beaudry and Spence, 1989, Clin. Exp. Hypertens. , 11, 943-956).

The compounds and compositions of the present invention due to their agonistic, particularly partial agonistic, property towards natural physiological ligands of the LXR

receptors, especially towards LXR-alpha, can serve as pharmaceuticals for controlling the biological effects of LXRs-mediated transcriptional control and the subsequent physiological effects produced thereby. More specifically they are capable of specifically modulating a cellular physiological response to reduce an associated pathology or provide or enhance a prophylaxis.

According to another embodiment, the compounds and compositions of the present invention are LXRs and/or LXRs LBD antagonists. According to another embodiment, the compounds and compositions of the present invention are specific antagonists towards LXR-alpha and/or LXR-alpha LBD. According to another embodiment, the compounds and compositions of the present invention are specific antagonists towards LXR-beta and/or LXR-beta LBD. By "antagonists" is meant a compound or composition which when combined with an intracellular receptor reduces or inhibits a reaction typical for the receptor, e.g., transcription activation activity. In one embodiment, said antagonists is a LXR-alpha antagonists, i.e. a LXR ligand which inhibits, reduces the transcriptional activity of a LXR-alpha receptor. One antagonist according to the present invention is the 6-(2,4-Dichloro-phenyl)-2-trifluoromethoxy-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinoline (CRX000935); or one of its pure enantiomer CRX001102 or CRX001059, preferably CRX001102.

Accordingly, the present invention further concerns a composition comprising at least one compound of the invention as disclosed above and a pharmaceutically acceptable carrier or diluent. These pharmaceutical compositions may be prepared by conventional techniques, e.g. as described in Remington, 1995, The Science and Practise of Pharmacy, 19.sup.th Ed.

Typical compositions of the present invention are associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, tablets, aerosols, solutions, suspensions or other container. In making the combination products, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compounds will usually be mixed with a carrier or a diluent, or diluted by a carrier or a diluent, or enclosed within a carrier or a diluent which may be in the form of a ampoule, capsule, sachet, paper, tablets, aerosols, solutions, suspensions or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compounds can be adsorbed on a granular solid container for example in a sachet. Typically, liquid oral pharmaceutical compositions are in the form of, for example, suspensions, elixirs and solutions; solid oral pharmaceutical compositions are in the form of, for example, powders, capsules, caplets, gelcaps and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed.

Some examples of suitable carriers or diluents are, without being limited, water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides,

pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone.

Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. The compound of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of lipids, including but not limited to amphipathic lipids such as phosphatidylcholines, sphingomyelins, phosphatidylethanolamines, phophatidylcholines, cardiolipins, phosphatidylserines, phosphatidylglycerols, phosphatidic acids, phosphatidylinositols, diacyl trimethylammonium propanes, diacyl dimethylammonium propanes, and stearylamine, neutral lipids such as triglycerides, and combinations thereof. They may either contain cholesterol or may be cholesterol-free.

These can be prepared according to methods known to those skilled in the art, for example, as described in US 4,522,811. The pharmaceutical compositions of the invention can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

The pharmaceutical compositions of the invention will typically be those which contain an effective amount of a compound of the invention, i.e. a LXRs modulating amount. As used herein, the term "LXRs modulating amount" refers to that amount of a compound that is needed to produce a desired effect in any one of the cell-based assays, biochemical assays or animal models described above. In general, an effective amount, or LXRs modulating amount, of a compound of the invention is a concentration of the said compound that will produce a 50% (EC_{50}) increase in LXR activity in a cell-based reporter gene assay, or a biochemical peptide sensor assay such as the assays described above (relative to an untreated control).

For example, the pharmaceutical compositions herein may contain between about 0.1 mg and about 1000 mg, preferably about 100 ug to about 500 mg, even more preferably about 5ug to about 50 mg, of the compound, advantageously about 10 mg and may be constituted into any form suitable for the mode of administration selected. The tablets or pills of the pharmaceutical composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be

delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, alcohol and cellulose acetate.

According to another embodiment, the compositions of the Invention may be advantageously combined and/or used in combination with at least one additional agent.

Examples of additional agent are other lipid-lowering or cholesterol-lowering agents, different from the compounds of the Invention. In many instances, administration in conjunction with the subject compositions enhances the efficacy of such agents. Exemplary cholesterol-lowering (hypocholesterolemic) and/or lipid-lowering (hypolipemic) agents include those above disclosed, such as bile acid sequestrants such as quaternary amines (e.g. cholestyramine and colestipol) or colesevelam; nicotinic acid and its derivatives (e.g. niacin) ; probucol ; Ezetimibe (Zetia™, Schering-Plough); HMG-CoA reductase inhibitors such as statins (e.g. mevastatin, lovastatin (Mevacor™, Merck), pravastatin (Pravachol™, Sankyo / Bristol-Myers Squibb), simvastatin (Zocor™, Merck), fluvastatin (Lescol™, Novartis), atorvastatin (Lipitor™, Pfizer), rosuvastatin (Crestor™, AstraZeneca), cerivastatin (Baycol™, Bayer) and pitavastatin); fibric acids such as clofibrate, gemfibrozil, bezafibrate, fenofibrate and ciprofibrate; probucol; raloxifene and its derivatives; and mixtures thereof.

Alternatively, the additional agent can be selected in the group consisting in natural or synthetic PPAR (alpha, beta and/or gamma) and/or FXR and/or RXR modulators (agonist or antagonist) and/or anti-inflammatory compounds (e.g. glucocorticoids).

Naturally occurring ligands that modulate the activity of PPAR, preferably the PPAR-gamma, include but are not

limited to, fatty acids such as arachidonic acid derivatives or metabolites such as eicosanoids (e.g. various isomeric forms of 8-hydroxytetraenoic acid) and cyclopentenone prostaglandins (e.g. prostaglandins in the J and A series and their metabolites), long-chain fatty acids and their derivatives, e.g. 9- and 13-cis-hydroxyoctadecadienoic acid (HODE) (Nagy et al., 1998, Cell, 17, 93, 229-240 ; Chinetti et al., 2001, Z. Kardiol, 90, Suppl 3, 125-32). Diterpene acids and auronols (e.g. pseudolaric acids A and B) isolated from Pseudolarix kaempferi (Pan et al., 1990, Planta. Med., 56, 383-385; Li et al., 1999, J. Nat. Prod., 62, 767-769) have also been shown to activate PPAR-gamma and are expected to be useful in the practice of this invention. In one embodiment, said natural PPAR ligand is a prostaglandin J2 or delta-12-prostaglandin J2 (PGJ2) metabolite, and more particularly it is 15-deoxy-delta-12,14-prostaglandin J2 [15-deoxy-Delta(12,14)-PGJ(2) or 15d-PGJ2].

Synthetic ligands that modulate the activity of PPAR are for example antidyslipidemic fibrates (e.g. clofibrate, fenofibrate, benzofibrate, ciprofibrate, gemfibrozil), thiazolidine derivatives (e.g. thiazolidinediones), glitazones (e.g. rosiglitazone), oxazolidine derivatives (e.g. oxazolidinediones), alpha-alkylthio, alpha-alkoxy and carboxylic acid derivatives of thiazolidines and oxazolidines (Hulin et al. 1996, J. Med. Chem., 39, 3897-3907), N-2-L-tyrosine derivatives (e.g. N-(2-Benzoylphenyl)-L-tyrosine ; Henke et al., 1998, J. Med. Chem., 41, 5020-5036), FMOC-L-Leucine (WO0200611), phenyl acetic acid derivatives (Berger et al., 1999, J. Biol. Chem., 274, 6718-6725) and indole-thiazolidinedione derivatives (Lohray et al., 1998, J. Med. Chem., 41, 1619-1630).

Compounds disclosed or described in the following articles, patents and patent applications which have FXR agonist activity are incorporated by reference herein: US

20020120137, US 20030181420, compound GW4064 (B. Goodwin et al., 2000, Molecular Cell 6, 517-526). Other examples of FXR agonists useful according to the present invention are bile acids (Chiang, 2002, Endocr. Rev., 23, 443-63).

Compounds disclosed or described in the following articles, patents and patent applications which have RXR agonist activity are incorporated by reference herein: US 5,399,586 and 5,466,861, WO96/05165, WO94/15901, WO93/11755, WO94/15902, WO93/21146, Boehm, et al. 1994, J. Med. Chem., 38, 3146-3155, Boehm, et al. 1994, J. Med. Chem., 37, 2930-2941, Antras et al., 1991, J. Biol. Chem., 1266, 1157-1161. RXR specific agonists include, but are not limited to, 9-cis-retinoic acid, 4-(1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-ethenyl)benzoic acid (3-methyl-TTNEB; LGD 1069), LG 100268 (i.e. 2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-cyclopropyl]-pyridine-5-carboxylic acid), 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthy)-2-carbonyl]-benzoic acid, ((E)-2-(2-((5,6,7,8-tetra-hydro-3,5,5,8,8-pentamethyl-2-naphthyl)propen-1- yl)-4-thiophenecarboxylic acid) (AGN 191701), 2-(5,6,7,8-tetra-hydro-5,5,8,8-tetramethyl-2-naphthyl)-2-(carboxyphenyl)-1 ,3-dioxolane (SR 11237), 4-(5H-2,3-(2,5-dimethyl-2,5-hemano)-5-methyl-dibenzo(b,e) (1,4)diazepin-11-yl)-benzoic acid (HX600) or thiadiazepin analogues thereof, 3,7,11,15-tetramethyl hexadecanoic acid (phytanic acid), 6-(1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl) nicotinic acid, ALRT 1057 (i.e. 9-cis retinoic acid, 2-(4-carboxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalen yl)-1,3-dithiane (SR11203), 4-(2-methyl)-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2- naphthalenyl)propenyl)benzoic acid (SR11217), and the like or a pharmaceutically acceptable salt thereof.

Other examples of additional agents which can be comprised in, or alternatively be used in combination with, the compositions of the Invention are antidiabetic and/or hypoglycemic agents (e.g. sulfonylurea or/and biguanide derivatives), insulin, insulin derivative, insulin secretagogue, insulin sensitizer, or insulin mimetic or those listed above (such as glitazones, PPAR modulators, etc…); other examples are mitotic inhibitors, alkylating agents, antimetabolites, nucleic acid intercalating agents, topoisomerase inhibitors, agents which promote apoptosis, or agents which increase immune responses to tumors (e.g cytokine chosen from alpha-, beta- and gamma-interferon, interleukins, and in particular IL-2, IL-4, IL-6, IL-10 or IL-12, tumour necrosis factors (TNFs) and colony stimulating factors (for example GM-CSF, C-CSF and M-CSF). Literature provides to the skilled man with numerous examples of such additional agents.

According to the present invention, the terms "used in combination with" mean that the compound of the Invention can be used simultaneously or consecutively or so as to be staggered over time. Simultaneously refers to a co-administration. In this case, the separate components of the combination can be mixed to form a single composition prior to being administered, or can be administered at the same time to the patient. It is also possible to administer them consecutively, that is to say one after the other, irrespective of which component of the combination according to the invention is administered first. Finally, it is possible to use a mode of administration which is staggered over time or is intermittent and which stops and restarts at intervals which may or may not be regular. It is pointed out that the routes and sites of administration of the two components can be different. The time interval between the administrations is not critical and can be defined by the

skilled person. It is possible to recommend an interval of from 10 min to 72 h, advantageously of from 30 min to 48 h, preferably of from 1 to 24 h and, very preferably, of from 1 to 6 h.

Another aspect of the present invention is a method for modulating the LXRs functions in a cell, a tissue and/or a patient in need thereof. According to this method, the cell, tissue or patient is contacted with a sufficient concentration of at least one compound or composition of the Invention for either an agonistic (including partial agonistic) or antagonistic effect to be detected. In particular embodiment, the Invention concerns a method for modulating the LXR-alpha and/or LXR-beta functions in a cell, a tissue and/or a patient in need thereof. In preferred case, the Invention concerns a method for modulating the LXR-alpha functions in a cell, a tissue and/or a patient in need thereof.

In yet another aspect, the present invention concerns a method for increasing the expression of at least one LXRs target gene, more specifically a LXR-alpha target gene, involved in cholesterol trafficking in a cell, a tissue and/or a patient in need thereof. According to this method, the cell, tissue or patient is contacted with a sufficient concentration of at least one compound or composition of the Invention for increased expression of at least one LXRs target genes involved in cholesterol trafficking to be detected. According to another embodiment, the present invention concerns a method for increasing the expression of at least one LXRs target gene involved in cholesterol trafficking in a cell, a tissue and/or a patient in need thereof, wherein the cell, tissue or patient is contacted with a sufficient concentration of at least one partial agonist, and more specifically with a sufficient concentration of at least one partial agonist of the

Invention or composition (including combination) comprising it. According to another embodiment, the present invention concerns a method for increasing the expression of at least one LXRs target gene involved in cholesterol trafficking in a cell, a tissue and/or a patient in need thereof, wherein the cell, tissue or patient is contacted with a sufficient concentration of at least one partial LXR-alpha agonist, said partial agonist having a Vmax of about 60%. In special embodiment, said partial agonist having a Vmax of about 60% is a partial LXR-alpha agonist of the Invention or a composition (including combination) comprising it.

"LXRs target genes involved in cholesterol trafficking" means a gene the expression of which is, at least partially, controlled by LXRs, and the expression product of which is implicated in the cholesterol transport efflux, and more specifically in the Reverse Cholesterol Transport (RCT). In special embodiments, said "LXRs target genes involved in cholesterol trafficking" is a gene the promoter of which comprises at least one LXR response element and the expression product of which is implicated in the cholesterol transport efflux, and more specifically in the Reverse Cholesterol Transport (RCT)[see e.g., Kwiterovich, 2000, Am. J. Cardiol., 86, 5L-10L]. Preferably, said LXRs target gene is selected in the group consisting of ATP-binding cassette transporters A1 (ABCA1), G1 (ABCG1), G5 (ABCG5) and G8 (ABCG8).

In yet another aspect, the present invention concerns a method for modulating expression of a gene involved in cholesterol trafficking. Preferably, said gene is selected in the group consisting of ATP-binding cassette transporters A1 (ABCA1), G1 (ABCG1), G5 (ABCG5), G8 (ABCG8), ApoE, LPL, PLTP and CETP.

In yet another aspect, the present invention concerns a method for increasing the expression of at least one LXRs target genes involved in cholesterol trafficking with a limited ability to increase or repress the expression of at least one LXRs target genes involved in lipogenesis in a cell, a tissue and/or a patient in need thereof. According to this method, the cell, tissue or patient is contacted with a sufficient concentration of at least one compound or composition of the Invention for increased expression of at least one LXRs target genes involved in cholesterol trafficking to be detected. "LXRs target genes involved in lipogenesis" means a gene the expression of which is, at least partially, controlled by LXRs, and the expression product of which is implicated in lipogenesis, and more specifically in triglycerides synthesis. In special embodiments, said "LXRs target genes involved in lipogenesis" is a gene the promoter of which comprises at least one LXR response element and the expression product of which is implicated in lipogenesis, and more specifically in triglycerides synthesis. In preferred embodiment, said LXRs target genes involved in lipogenesis is selected in the group consisting of FAS, SREBP1c, SCD-1, ACC and Angptl3.

In yet another aspect, the present invention concerns a method for modulating expression of a gene involved in lipogenesis. In preferred embodiment, said gene is selected in the group consisting of FAS, SREBP1c, SCD-1, ACC and Angptl3.

"Ability to increase or limited ability to increase the expression of at least one LXRs target genes" are as defined above.

The compounds and compositions (including combinations with additional agent, see above) of the present invention are specially adapted to provide a desired therapeutic or

prophylactic effect for a given LXRs-mediated condition. Accordingly, a further aspect of the present invention is a method for the treatment of a patient, including man, in particular in the treatment of diseases and conditions where modification of the effects of LXRs, including LXR-alpha and/or LXR-beta, is of therapeutic benefit, the method comprising administering to the patient in need a therapeutically effective amount of at least one compound of the Invention, or a pharmaceutically composition (including combination with additional agent) as above disclosed. According to another embodiment, the present invention concerns a method for the treatment of a patient, including man, in particular in the treatment of diseases and conditions where modification of the effects of LXRs, including LXR-alpha and/or LXR-beta, is of therapeutic benefit, the method comprising administering to the patient in need a therapeutically effective amount of at least one partial agonist, and more specifically with a therapeutically effective amount of at least one partial agonist of the Invention or composition (including combination with additional agent) comprising it. According to another embodiment, the present invention concerns a method for the treatment of a patient, including man, in particular in the treatment of diseases and conditions where modification of the effects of LXRs, including LXR-alpha and/or LXR-beta, is of therapeutic benefit, the method comprising administering to the patient in need a therapeutically effective amount of at least one partial LXR-alpha agonist, said partial agonist having a Vmax of about 60%. In special embodiment, said partial agonist having a Vmax of about 60% is a partial LXR-alpha agonist of the Invention or a composition (including combination with additional agent) comprising it.

It will be appreciated by those skilled in the art that the term "treatment" herein extends to prophylaxis as well as the treatment of established diseases or symptoms.

"Diseases and conditions where modification of the effects of LXRs is of therapeutic benefit" means LXRs-mediated diseases or pathologic conditions wherein the observed disorder is associated, at least partially, with the deregulation, disturbance, hypersensitivity, or malfunctioning of cells expressing LXR nuclear receptors, or more specifically in which the disease or pathologic conditions is caused by one or more genes that are under the transcription control of LXRs, or said disease or pathological condition causing genes are post-translationally modified in response to the treatment with an LXRs ligand. These diseases and conditions are further called "diseases and conditions which can be controlled by LXRs". Examples of these cells are those from liver, skeletal muscle, kidney, skin, heart, CNS, adipose tissues, spleen, intestine, or cells of the monocyte lineage. In preferred embodiment, said cell type is a hepatocyte, an adipocyte, an intestinal cell or a macrophage.

Examples of these diseases or pathologic conditions are those associated with impaired metabolism of lipids, e.g. cholesterol and/or triglycerides, and more specifically those related to pathologic levels or ratios of lipids (e.g. dyslipidemia, including hyperlipidemia, dyslipoproteinemia, including hyperlipoproteinemia, hypertriglyceridemia, disorders related to cholesterol or bile acid metabolisms, including hypercholesterolemia, gall stone or gall bladder disorders) ; as well as vascular or inflammatory diseases or disorders (e.g. cardiovascular disease, including atherosclerotic cardiovascular diseases, coronary artery diseases, peripheral vascular diseases, cerebrovascular diseases, thrombotic disorders ,restenosis, rheumatoid

arthritis, or septic shock); diseases or disorders associated with malfunctioning (including deficiency) of the expression of at least one LXRs target gene; CNS diseases including those affecting cognitive function or age related disorders such as neurodegenerative diseases (e.g. Alzheimer's disease) ; diseases or disorders related to lipid storage such as obesity, diabetes (including type 2 diabetes and Syndrome X), hypertension ; pancreatitis ; skin proliferative disorders, including psoriasis, atopic dermatitis or acne ; sexual impotence, renal disease and cancers.

Hyperlipidemia's characteristics of raised plasma concentrations of triglyceride, raised low density lipoprotein cholesterol (LDL-c) concentrations, and low concentrations of high density lipoprotein cholesterol (HDL-c) are known independent risk factors for atherosclerosis and its clinical sequelae, ischemic heart disease or coronary heart disease. Atherogenesis is the process by which lipids accumulate in the intimal lining of arteries leading to the formation of plaques and hardening of the vessel wall or atherosclerosis. Although the exact mechanism leading to atherogenesis is still not well understood, abnormalities of lipid and lipoprotein metabolism, coagulation, hyperinsulinism and glycation all seem to contribute significantly to the process (Bierman, E. L., Arterio. Throm. 12:647-656 (1992)). Hyperlipidemia in clinical practice, defined by the upper 10 percent of the distribution of plasma lipid levels in a population, i.e., serum cholesterol of 205 mg/dl or higher, serum triglycerides of 200 mg/dl, is usually recommended for treatment. Routine measurements of concentrations of cholesterol and triglycerides in the plasma have become widespread in clinical practice which permits the identification of patients with asymptomatic hyperlipidemia. Guidelines are available for diagnosis and monitoring responses to therapy. The lowering of plasma lipid

concentrations reduces the number and size of atherogenic plaques on the intima of blood vessels.

Thus, in yet another aspect, the Invention concerns a method for the treatment of hyperlipidemia, obesity, type II diabetes, atherosclerosis, ischemic heart disease, peripheral vascular disease, cerebral vascular disease, hypercholesterolemia, hypertriglyceridemia, pancreatitis or coronary artery disease or hyperlipoproteinemia using at least one compound or pharmaceutical compositions (including combinations with additional agent) of the Invention. According to another embodiment, the present invention concerns a method for the treatment of hyperlipidemia, obesity, type II diabetes, atherosclerosis, ischemic heart disease, peripheral vascular disease, cerebral vascular disease, hypercholesterolemia, hypertriglyceridemia, pancreatitis or coronary artery disease or hyperlipoproteinemia using at least one partial LXR-alpha agonist, and more specifically at least one partial agonist of the Invention or composition (including combination with additional agent) comprising it. According to another embodiment, the present invention concerns a method for the treatment of hyperlipidemia, obesity, type II diabetes, atherosclerosis, ischemic heart disease, peripheral vascular disease, cerebral vascular disease, hypercholesterolemia, hypertriglyceridemia, pancreatitis or coronary artery disease orhyperlipoproteinemia using at least one partial LXR-alpha agonist, said partial agonist having a Vmax of about 60%. In special embodiment, said partial LXR-alpha agonist having a Vmax of about 60% is a partial agonist of the Invention or a composition comprising it. Briefly, this aspect of the invention involves administering to a patient in need of such treatment an amount of at least one compound or a composition (including combination with additional agent) of the invention, or of at least one partial agonist having a Vmax

of about 60%, in effective to lower the total plasma cholesterol level of said subject. Preferably, said amount is effective to lower the LDL-c and more preferably also to increase the HDL-c levels in said patient. Even more preferably, said amount is effective to lower the LDL-c, and more preferably to additionally increase the HDL-c levels in said patient, without increasing the TG level (measured in plasma and/or liver). As employed herein, the phrase "amount... effective to" refers to levels of compound of the present invention sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10 nM up to 2 uM; with concentrations in the range of about 100 nM up to 500 nM being preferred. As noted previously, since the activity of different compounds of the present invention which fall within the definition of structure I as set forth above may vary considerably, and since individual subjects may present a wide variation in severity of symptoms, it is up to the practitioner to determine a subject's response to treatment and vary the dosages accordingly.

In yet another aspect, the Invention concerns a method for the enhancement of the Reverse Cholesterol Transport (RCT) in a patient in need by administering at least one compound, a composition or a combination of the invention.

In yet another aspect, the Invention concerns a method for lowering the atherosclerosis plaque in a patient in need by administering at least one compound, a composition or a combination of the invention.

In yet another aspect, the Invention concerns a method for reducing the risk for coronary heart disease by improving levels of HDL-cholesterol (HDLc), reducing the levels of triglycerides (TG) with the potential to reduce LDL-cholesterol (LDL-c) in a patient in need by administering at

least one compound, a composition or a combination of the invention.

In another embodiment, disease or pathologic condition according to the invention is an inflammatory disease including, but not limited to, T-lymphocyte activation and other T-lymphocyte-related disorders ; inflammatory cytokine (e.g. TNF-alpha, interleukin (IL)-1-alpha, IL-1-beta, IL-2, IL-6) production ; activation of nuclear factors that promote transcription of genes encoding inflammatory cytokines. Examples of these nuclear transcription factors include but are not restricted to, nuclear factor-kappaB (NF-kappaB), activated protein-1 (AP-1), nuclear factor of activated T cells (NFAT).

Alternatively, the present invention concerns a method of treating and/or preventing diseases or conditions in a patient, comprising the step of administering to said individual a pharmacologically effective dose of a compound or composition (including combination with additional agent) of the invention said administration resulting in improving the clinical status of said patient.

According to the present invention, the term "patient" means a mammal, e.g., a primate, e.g., a human.

By "pharmaceutically effective dose" is meant an amount of a pharmaceutical compound or composition having a therapeutically relevant effect in the frame of treatment and/or prevention of conditions mediated by LXRs such as those disclosed above. A therapeutically relevant effect relieves to some extent one or more symptoms of conditions mediated by LXRs in a patient or returns to normal either partially or completely one or more physiological or biochemical parameters associated with or causative of said conditions, e.g. hypercholesteremia, hypertriglyceridemia, total cholesterol, HDLc, LDLc and/or TG levels, etc... In a

preferred embodiment, a pharmaceutically effective dose of a compound or composition (including combination with additional agent) means an amount that decreases total cholesterol, decreases LDL-c, preferably also increases HDL-c, and advantageously does not increase TG levels (measured in plasma and/or liver of the treated patient). The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a dosage of about 2 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, on the therapeutic effect that is intended to be achieved, the form in which the dosage is administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge. Dosages and treatment schedules are readily attainable by routine experimentation to those having ordinary skill in this art. Generally, the compounds are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

The compounds or compositions (including combinations with additional agent) of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Similarly, the treatment can be adapted to administer the compounds or compositions (including combinations) of the invention in a single weekly or monthly dose. Moreover, it will be appreciated that the amount of a

compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02 - 5000 mg per adult human per day, e.g., 1-1500 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about 30 mg/kg of body weight per day. Particularly, the range is from about 0.03 to about 15 mg/kg of body weight per day, and more particularly, from about 0.05 to about 10 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 2 times per day. Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

Toxicity and therapeutic efficacy of the compounds included in the compound or composition of the invention can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic

effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, special care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, leads to a reduction of side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

The route of administration of the compound or composition of the present invention may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral or intratumoral route being preferred.

The present invention further concerns compounds and compositions (including combinations with additional agent) of the present invention for use in therapy. Similarly, it concerns the use of at least one compound or composition (including combinations with additional agent) according of the present invention for the manufacture of a medicament for the treatment of diseases and conditions where modification of the effects of LXRs is of therapeutic benefit (see above). It further concerns the use of at least one partial LXR-alpha agonist, said partial agonist having a Vmax of about 60%, for the manufacture of a medicament for the treatment of diseases and conditions where modification of the effects of LXRs is of therapeutic benefit. Examples of these diseases and conditions are provided above.

According to a preferred embodiment, the present invention concerns the use of at least one compound or composition (including combinations with additional agent) according of the present invention for the manufacture of a medicament for the treatment of individuals requiring lower total cholesterol levels and/or TG level.

Compounds of the general formula (I) and/or (II) above described can be prepared using readily available starting materials or known intermediates. Specific methods are provided in the Experimental Section.

The compounds and compositions (including combinations with additional agent) of the present invention may also find use in a variety of *in vitro* and *in vivo* assays, including diagnostic assays. For example, various allotypic LXRs gene expression processes may be distinguished in sensitivity assays with the subject compounds and compositions, or panels thereof. In certain assays and in *in vivo* distribution studies, it is desirable to use labeled versions of the subject compounds and compositions, e.g. in radioligand

displacement assays. Accordingly, the invention provides the compounds and compositions of the invention comprising a detectable label, which may be spectroscopic (e.g. fluorescent), radioactive, etc.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

The invention has been described in an illustrative manner, and it is to be understood that the terminology which has been used is intended to be in the nature of words of description rather than of limitation. Obviously, many modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practised otherwise than as specifically described. Accordingly, those skilled in the art will recognize, or able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

These and other embodiments are disclosed or are obvious from and encompassed by the description and examples of the present invention. Further literature concerning any one of

the methods, uses and compounds to be employed in accordance with the present invention may be retrieved from public libraries, using for example electronic devices. For example the public database "Medline" may be utilized which is available on Internet, e.g. under http://www.ncbi.nlm.nih.gov/PubMed/medline.html. Further databases and addresses, such as http://www.ncbi.nlm.nih.gov/, http://www.infobiogen.fr/, http://www.fmi.ch/biology/research_tools.html, http://www.tigr.org/, are known to the person skilled in the art and can also be identified/located using, e.g., http://www.lycos.com. An overview of patent information in biotechnology and a survey of relevant sources of patent information useful for retrospective searching and for current awareness are given in Berks, TIBTECH 12 (1994), 352-364.

FIGURE LEGENDS

Figure 1 : Dose response assay of CRX156651 in CV1 transfection assays using a human LXR alpha expression plasmid and luciferase reporter plasmid containing five copies of LXR response element.

Figure 2 : CRX156651 dose response induction of ABCA1 gene expression in THP-1 cells as determined by real time PCR.

Figure 3 : CRX156651 dose response induction of FAS (Fig. 3A) and SREBP1c (Fig. 3B) gene expression in HepG-2 cells as determined by real time PCR.

Figure 4 : CRX156651 dose response induction of Angtpl3 gene expression in HepG-2 cells as determined by real time PCR.

Figure 5 : ApoAI specific cholesterol efflux in differentiated THP-1 cells.

Figure 6 : HDL cholesterol plasma levels change following 10 mg/kg CRX156651 oral administration to C57BL/6 male mice for 7 days (n=6, p=0.003).

Figure 7 : Plasma (Fig.7A) and liver triglyceride (Fig.7B) levels do not change following 10 mg/kg CRX156651 oral administration to C57BL/6 male mice for 7 days (n=6, p=0.212 and p=0.365, respectively). In the same experiment, these parameters are significantly increased compared to the T0901317 (p=0.016 and p=0.002, respectively).

EXAMPLES

Material

Reference compounds

- **T0901317 (*N*-(2,2,2-trifluoro-ethyl)-*N*-[4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-phenyl]-benzenesulfonamide)** is a synthetic, nonsteroidal LXR-selective agonist presenting a high affinity towards LXR alpha (EC_{50} values of 20 nM) and beta (Schultz et al., 2000, Genes Dev. 14, 2831-2838) and possessing the capacity to activate LXRs *in vitro* during the transfection assays, to induce the cholesterol efflux *in vitro* (Laffitte et al., 2001, Mol Cell Biol. 21, 7558-7568) and to improve insulin sensitivity in diabetic animals (Cao et al., 2003, J Biol. Chem. 278, 1131-1136.). In addition, T0901317 possesses the capacity to induce lipogenesis *in vitro and in vivo* (Schultz, et al., 2000, Genes Dev. 14, 2831-2838; Joseph, et al., 2002, J Biol Chem. 277, 11019-11025).

- **GW3965** is a synthetic high affinity LXR alpha and beta ligand (Collins, et al., 2002, J Med Chem. 45, 1963-1966) that possesses the capacity to activate LXRs *in vitro* during the transfection assays, to induce both the

cholesterol efflux *in vitro* and *in vivo* (Collins, et al., 2002, J Med Chem. 45, 1963-1966) and to inhibit the development of atherosclerosis in atherosclerotic animal models (Joseph, et al., 2002, Proc Natl Acad Sci U S A. 99, 7604-7609). In addition, GW3965 possesses the capacity to induce lipogenesis *in vivo* (Joseph, et al., 2002, Proc. Natl. Acad. Sci. 99, 7604-7609).

Plasmids

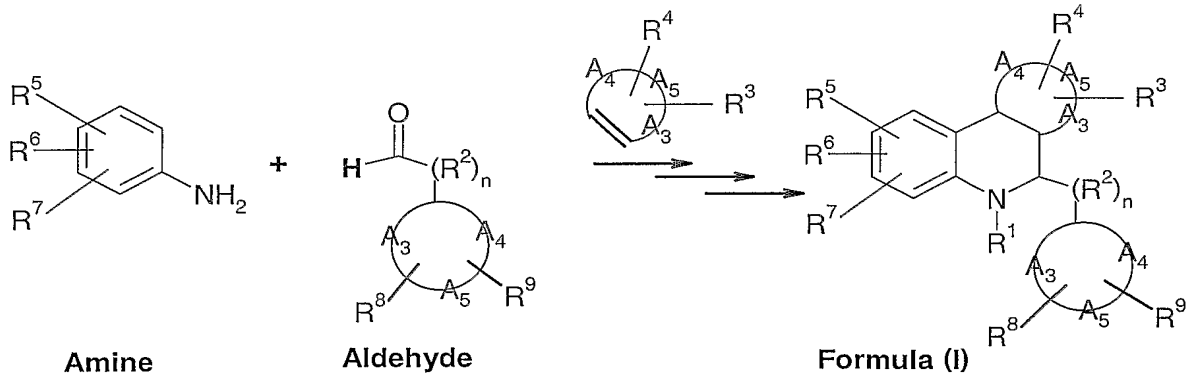
- hLXR alpha plasmid : expression vector encoding full length human LXR alpha .

- luciferase reporter plasmid : vector in which luciferase gene expression is placed under the control of a LXR response element.

- pCMV-betaGAL plasmid : control of transfection efficacy, it is a vector encoding beta-galactosidase gene.

Example 1. Compounds general synthesis

General Reaction Scheme:



Tetrahydroquinolines of formula (I) are obtained by an imino Diels-Alder reaction (Buonora and Olsen, 2001, Tetrahedron, 57, 6099-6138) such as described in the reaction scheme above.

This three components reaction is set with amines, aldehydes and appropriate dienophiles in suitable solvents, such as acetonitrile, dichloromethane, ether, THF, toluene, fluorinated alcohols, with acidic catalysis, such as TFA or Lewis Acid catalysts (chiral or not) and with heating where necessary (Spanedda et al., 2003, Tetrahedron Letters, 44, 217-219 ; Sundararajan et al., 2001, Organic Letters, 3, 1973-1976 ; Hadden et Stevenson, 1999, Tetrahedron Letters, 40 , 1215-1218 ; Babu et Perumal, 1998, Tetrahedron Letters, 39, 3225-3228).

Introduction of the R^1 group on the nitrogen is made according to methods known to those skilled in the art e.g. alkylation with benzyl bromide in the presence of a base or acylation with anhydride followed by reduction of the carbonyl.

If, in any of the other processes mentioned herein, the substituting moiety R^1, R^2, R^3, R^4, R^5, R^6 and/or R^7 is different from the one required, the substituting moiety may be converted to the desired moiety by known methods. The substituting moiety R^1, R^2, R^3, R^4, R^5, R^6 and/or R^7 may also need protection against the conditions under which reactions are carried out, accordingly, a protecting group may be used which is removed after reactions have been completed.

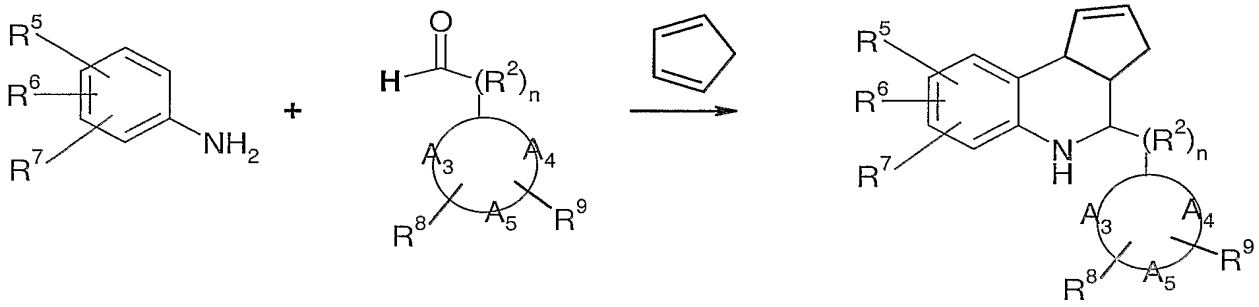
The individual isomers of [I] may be separated using, for example, column chromatography, HPLC or recrystallisation.

According to this Example, compounds of the invention CRX000935 (6-(2,4-Dichloro-phenyl)-2-trifluoromethoxy-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinoline) and CRX000973 (4-(2,4-Dichloro-phenyl)-1,2,3,9b-tetramethyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline) have been synthesized using this method using, respectively, as "three components" 2,4-

Dichloro-benzaldehyde, indene and 4-Trifluoromethoxy-phenylamine, and 2,4-Dichloro-benzaldehyde, 1,2,3,4-Tetramethyl-cyclopenta-1,3-Diene and 4-Trifluoromethoxy-phenylamine.

Example 2 : Synthesis of cyclopenta[c]quinoline of the invention (WO98/27427)

Scheme 1 : general synthesis protocol



Amine Aldehyde Cyclopenta[c]quinoline

TFA (0.9 eq) is added drop wise to a solution of amine [(R^5, R^6, R^7)-phenyl amine] (1 eq) in CH_3CN. Cyclopentadiene (4 eq) freshly distillated and dissolved in CH_3CN is added. Finally, aldehyde (1 eq) is added drop wise.

The mixture is stirred at room temperature for 4 to 48 hours, and the solvent is removed under vacuum. The residue is dissolved in ethyl acetate and washed with a saturated aqueous solution of $NaHCO_3$. The crude product is purified by column chromatography with heptane/ethyl acetate (7/3) or heptane/methylene chloride (6/4) as eluent to afford the compound.

Example 2.1 Said protocol has been implemented for preparing the following compounds of the invention :

Amine	Aldehyde	Cyclopenta (c) quinoline (compound of Formula I)	CRX number
1-(4-Amino-phenyl)-ethanone	2,3-Dichloro-benzaldehyde	1-[4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanone	CRX156538
4-Trifluoro methoxy-phenylamine	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX156651
1-(4-Amino-phenyl)-ethanone	2-Chloro-benzaldehyde	1-[4-(2-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanone	CRX156540
4-Trifluoro methoxy-phenylamine	4-Nitro-benzaldehyde	4-(4-Nitro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX156612
4-Amino-benzoic acid ethyl ester	2-(2-Vinyl-phenyl)-but-2-enal	4-Naphthalen-1-yl-3a,4,5,9b-tetrahydro-3Hcyclopenta[c]quinoline-8-carboxylic acid ethyl ester	CRX123501
1-(4-Amino-phenyl)-ethanone	2,4-Dichloro-benzaldehyde	1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanone	CRX156545
4-Amino-benzoic acid ethyl ester	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	CRX123485
4-Amino-benzoic acid ethyl ester	4-Nitro-benzaldehyde	4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	CRX123457

4-Amino-benzoic acid ethyl ester	2-Chloro-benzaldehyde	4-(2-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	CRX123489
4-Amino-benzoic acid ethyl ester	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	CRX125053
4-Nitro-phenylamine	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-8-nitro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX156528
4-Chloro-phenylamine	2-Chloro-benzaldehyde	8-Chloro-4-(2-chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX156533
4-Methoxy-phenylamine	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-8-methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX156584
4-Amino-benzoic acid methyl ester	4-Nitro-benzaldehyde	4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid methyl ester	CRX125080
4-Amino-benzoic acid ethyl ester	4-Chloro-benzaldehyde	4-(4-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	
2-Amino-benzoic acid ethyl ester	2-Bromo-benzaldehyde	4-(2-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid ethyl ester	
2-Amino-	4-Bromo-	4-(4-Bromo-phenyl)-3a,4,5,9b-tetrahydro-	

benzoic acid ethyl ester	benzaldehyde	3H-cyclopenta[c]quinoline-6-carboxylic acid ethyl ester	
4-Amino-benzoic acid ethyl ester	3-Bromo-benzaldehyde	4-(3-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	
4-Trifluoro methoxy-phenylamine	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000292
4-Trifluoro methoxy-phenylamine	Benzaldehyde	4-Phenyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000293
4-Trifluoro methoxy-phenylamine	2,4-Dichloro-benzaldehyde	1-[4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl]-2,2,2-trifluoro-ethanone	CRX 000295
4-Trifluoro methoxy-phenylamine	2-Furaldehyde	4-Furan-2-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000319
2-(4-Amino-phenyl)-1,1,1,3,3,3-hexa fluoro-propan-2-ol	2,4-Dichloro-benzaldehyde	2-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol	CRX 000321
2-(4-Amino-phenyl)-1,1,1,3,3,3-hexa fluoro-propan-2-ol	2,3-Dichloro-benzaldehyde	2-[4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol	CRX 000322
4-Methoxy-phenylamine	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-8-methoxy-3a,4,5,9b-tetrahydro-3H-	CRX 000361

		cyclopenta[c]quinoline	
4-Hydroxy-phenylamine	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-ol	CRX 000368
4-Trifluoro methyl-phenylamine	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000369
4-Trifluoro methyl-phenylamine	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000370
4-Trifluoro methoxy-phenylamine	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000374
1-(4-Amino-phenyl)-ethanone	2-Furaldehyde	1-(4-Furan-2-yl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)-ethanone	CRX 000387
4-Trifluoro methoxy-phenylamine	Thiophene-2-carbaldehyde	4-Thiophen-2-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000406
4-Trifluoro methoxy-phenylamine	2,6-Dichloro-benzaldehyde	4-(2,6-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000409
4-Trifluoro methoxy-phenylamine	Naphthalene-1-carbaldehyde	4-Naphthalen-1-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000412

4-Trifluoro methoxy-phenylamine	Phenyl-acetaldehyde	4-Benzyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000413
4-Trifluoro methoxy-phenylamine	Cyclohexanecarbaldehyde	4-Cyclohexyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000415
4-Trifluoro methoxy-phenylamine	2,4-Dichloro-benzaldehyde	5-Benzyl-4-(2,4-dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000416
4-Trifluoro methoxy-phenylamine	Thiophene-3-carbaldehyde	4-Thiophen-3-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000429
4-Trifluoro methoxy-phenylamine	Thiazole-2-carbaldehyde	4-Thiazol-2-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000430
4-Trifluoro methoxy-phenylamine	Pyridine-4-carbaldehyde	4-Pyridin-4-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000507
4-Trifluoro methoxy-phenylamine	5-Phenyl-thiophene-2-carbaldehyde	4-(5-Phenyl-thiophen-2-yl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000508
4-Amino-benzoic acid ethyl ester	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	CRX 000525
4-Amino-benzoic acid ethyl ester	Benzaldehyde	4-Phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	CRX 123505
4-Trifluoro methoxy-phenylamine	2-Methoxy-benzaldehyde	4-(2-Methoxy-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-	CRX 000558

		3H-cyclopenta[c]quinoline	
4-Trifluoro methoxy-phenylamine	2-Chloro-4-fluoro-benzaldehyde	4-(2-Chloro-4-fluoro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000564
4-Trifluoro methoxy-phenylamine	2-Nitro-benzaldehyde	4-(2-Nitro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000567
4-Trifluoro methoxy-phenylamine	Biphenyl-4-carbaldehyde	4-Biphenyl-4-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000568
4-Trifluoro methoxy-phenylamine	2-chloro-benzaldehyde	4-(2-Chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000569
4-Trifluoro methoxy-phenylamine	4-chloro-benzaldehyde	4-(4-Chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000570
4-Trifluoro methoxy-phenylamine	3-Fluoro-2-methyl-benzaldehyde	4-(3-Fluoro-2-methyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000593
4-Trifluoro methoxy-phenylamine	2-Ethyl-benzaldehyde	4-(2-Ethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000595
4-Trifluoro methoxy-phenylamine	2,3-Dimethyl-benzaldehyde	4-(2,3-Dimethyl-phenyl)-8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000596
4-Trifluoro methoxy-phenylamine	2-Trifluoro methyl-benzaldehyde	8-Trifluoromethoxy-4-(2-trifluoromethyl-phenyl)-3a,4,5,9b-	CRX 000612

		tetrahydro-3H-cyclopenta[c]quinoline	
4-Trifluoro methoxy-phenylamine	2-Fluoro-3-trifluoro methyl-benzaldehyde	4-(2-Fluoro-3-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000613
4-Trifluoro methoxy-phenylamine	2-Chloro-4-dimethyl amino-benzaldehyde	[3-Chloro-4-(8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenyl]-dimethyl-amine	CRX 000614
4-Trifluoro methoxy-phenylamine	2-Chloro-3-trifluoro methyl-benzaldehyde	4-(2-Chloro-3-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX 000646

Example 2.2 The following compounds were obtained by the same protocol:

Amine	Aldehyde	Cyclopenta (c) quinoline (compound of Formula I)	CRX number	Analysis
4-Trifluoro methoxy-phenyl amine	Formaldehyde	8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000320	ESI(+) =256
4-Trifluoro methoxy-phenyl amine	3-Nitro-benz aldehyde	4-(3-Nitro-phenyl)-8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000323	Mp =148°C
4-Trifluoro	Acet aldehyde	4-Methyl-8-trifluoromethoxy-	CRX 000408	ESI(+) =470

methoxy-phenyl amine		3a,4,5, 9b-tetrahydro-3H-cyclopenta[c] quinoline		
4-Trifluoro methoxy-phenyl amine	2,2-Dimethyl-propion aldehyde	4-tert-Butyl-8-trifluoromethoxy-3a, 4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000410	ESI(-) =410
4-Trifluoro methoxy-phenyl amine	Oxo-acetic acid ethyl ester	8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline-4-carboxylic acid ethyl ester	CRX 000414	Mp =90°C
4-Trifluoro methoxy-phenyl amine	4-Fluoro-2-trifluoro methyl-benz aldehyde	4-(4-Fluoro-2-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000740	ESI(+) =418
4-Trifluoro methoxy-phenyl amine	4-Trifluoro methoxy-benz aldehyde	8-Trifluoromethoxy-4-(4-trifluorome thoxy-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000741	ESI(+) =416
4-Trifluoro methoxy-phenyl amine	4-Ethyl-benz aldehyde	4-(4-Ethyl-phenyl)-8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclo penta[c]quinoline	CRX 000742	ESI(+) =360
4-Trifluoro methoxy-	2-Chloro-4-hydroxy-	3-Chloro-4-(8-trifluoromethoxy-3a,4	CRX 000743	ESI(+) =382

phenyl amine	benz aldehyde	,5,9b-tetrahydro-3H-cyclopenta[c] quinolin-4-yl)-phenol		
4-Trifluoro methoxy-phenyl amine	2,4-Bis-trifluoro methyl-benz aldehyde	4-(2,4-Bis-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000744	ESI(+) =468
4-Trifluoro methoxy-phenyl amine	2-Fluoro-4-trifluoro methyl-benzalde hyde	4-(2-Fluoro-4-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000745	APCI(+)=418
4-Trifluoro methoxy-phenyl amine	3,5-Dichloro-pyridine-4-carb aldehyde	4-(3,5-Dichloro-pyridin-4-yl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000763	ESI(+) =401
4-Trifluoro methoxy-phenyl amine	2,4-Dichloro-benz aldehyde	4-(3,4-Dichloro-phenyl)-8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000764	ESI(+) =400
4-Trifluoro methoxy-phenyl amine	Cycloprop anecarb aldehyde	4-Cyclopropyl-8-trifluoromethoxy-3a ,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000863	ESI(+) =296
4-Trifluoro methoxy-phenyl	Piperidin e-4-carb aldehyde	4-Piperidin-4-yl-8-trifluoromethoxy -3a,4,5,9b-	CRX 000899	ESI(+) =339

amine		tetrahydro-3H-cyclopenta [c]quinoline		
4-Trifluoro methoxy-phenyl amine	2-Chloro-4-methoxy-benz aldehyde	4-(2-Chloro-4-methoxy-phenyl)-8-tri fluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000903	ESI(+) =396
4-Trifluoro methoxy-phenyl amine	4-Formyl-piperidine-1-carboxylic acid tert-butyl ester	4-(8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin-4-yl)-piperidine-1-carboxylic acid tert-butyl ester	CRX 000905	ESI(+) =439
Phenyl amine	2,4-Dichloro-benz aldehyde	4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000737	ESI(+) =316
4-Amino-phenol	2,4-Dichloro-benz aldehyde	4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin-8-ol	CRX 000738	ESI(+) =332
p-Tolyl amine	2,4-Dichloro-benz aldehyde	4-(2,4-Dichloro-phenyl)-8-methyl-3a ,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000739	ESI(+) =330
4-Amino-benzo nitrile	2,4-Dichloro-benz aldehyde	4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline -8-carbonitrile	CRX 000746	Mp = 199°C
(4-Amino-phenyl)-acetic	2,4-Dichloro-benz	[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-	CRX 000747	Mp = 209°C

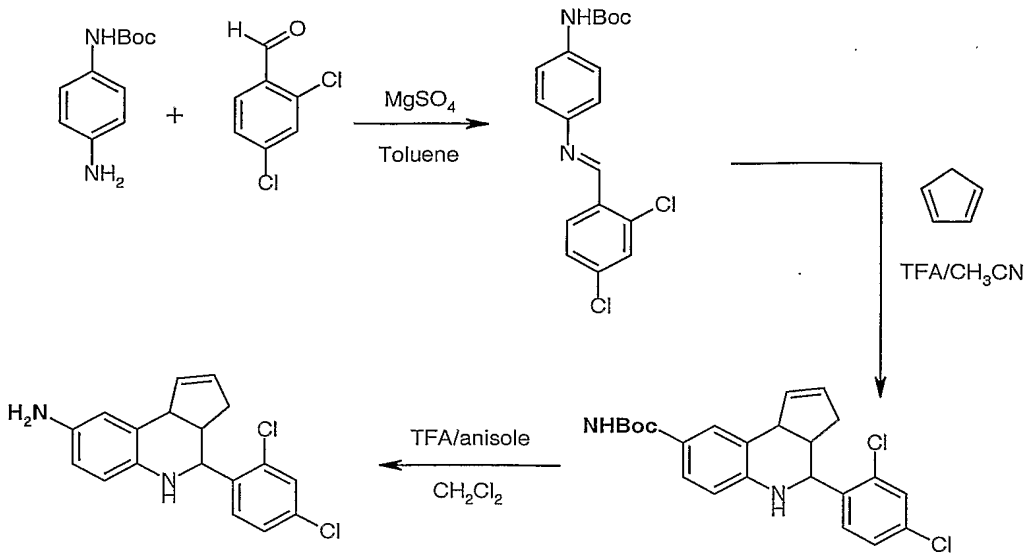
acid	aldehyde	tetrahydro-3H-cyclopenta[c] quinolin -8-yl]-acetic acid		
N,N-Dimethyl-benzene-1,4-diamine	2,4-Dichloro-benz aldehyde	[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin -8-yl]-dimethyl-amine	CRX 000794	ESI(+) =359
(4-Amino-phenyl)-methanol	2,4-Dichloro-benz aldehyde	[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin -8-yl]-methanol	CRX 000896	ESI(+) =346
4-Trifluoro methyl-phenylamine	Cyclohexanecarb aldehyde	4-Cyclohexyl-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000977	APCI(+)=322
4-Trifluoro methyl-phenyl amine	4-Fluoro-2-trifluoro methyl-benz aldehyde	4-(4-Fluoro-2-trifluoromethyl-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000997	APCI(+)=402
4-Trifluoro methyl-phenyl amine	2-Nitro-benz aldehyde	4-(2-Nitro-phenyl)-8-trifluoro methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 001000	APCI(+)=361
2-Chloro-4-trifluoro methoxy-phenyl amine	2,4-Dichloro-benz aldehyde	6-Chloro-4-(2,4-dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]	CRX 001066	Mp = 180°C

		quinoline		
N-(4-Amino-phenyl)-methane Sulfon amide	2,4-Dichloro-benz aldehyde	N-[4-(2,4-Dichloro-phenyl)-3a,4,5,9 b-tetrahydro-3H-cyclopenta[c] quinolin-8-yl]-methane sulfonamide	CRX 001018	ESI(+) =409
2-(4-Amino-phenyl)-1,1,1,3,3,3-hexa fluoro-propan-2-ol	Form aldehyde	1,1,1,3,3,3-Hexafluoro-2-(3a,4,5,9b -tetrahydro-3H-cyclopenta[c] quinolin-8-yl)-propan-2-ol	CRX 000971	Mp= 128°C
2-(4-Amino-phenyl)-1,1,1,3,3,3-hexa fluoro-propan-2-ol	4-Fluoro-2-trifluoro methyl-benz aldehyde	1,1,1,3,3,3-Hexafluoro-2-[4-(4-fluoro-2-trifluoromethyl-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin-8-yl]-propan-2-ol	CRX 000860	APCI(+)=500
2-(4-Amino-phenyl)-1,1,1,3,3,3-hexa fluoro-propan-2-ol	Cyclo Hexane carbaldeh yde	2-(4-Cyclohexyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin-8-yl)-1,1,1,3,3,3-hexafluoro-propan-2-ol	CRX 000861	ESI(+) = 420
3-Trifluoro methoxy-phenyl amine	2,4-Dichloro-benz aldehyde	4-(2,4-Dichloro-phenyl)-7-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 000792	ESI(+) = 400
4-	2,4-Bis-	4-(2,4-Bis-	CRX 000969	ESI(+)

Trifluoro methoxy-phenyl amine	trifluoro methyl-benz aldehyde	trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetra hydro-3H-cyclopenta[c] quinoline		= 468
2-Chloro-4-trifluoro methyl-phenyl amine	2,4-Dichloro-benz aldehyde	6-Chloro-4-(2,4-dichloro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 001083	ESI(+) = 418
3-Chloro-4-trifluoro methoxy-phenyl amine	2,4-Dichloro-benz aldehyde	7-Chloro-4-(2,4-dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 001084	ESI(+) = 434
2-Chloro-4-trifluoro methoxy-phenyl amine	4-Fluoro-2-trifluoro methyl-benz aldehyde	6-Chloro-4-(4-fluoro-2-trifluoro methyl-phenyl)-8-trifluoromethoxy-3a,4 ,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 001087	ESI(+) = 452
2-Chloro-4-trifluoro methoxy-phenyl amine	Benz aldehyde	6-Chloro-4-phenyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 001088	ESI(+) = 366
2-Chloro-4-trifluoro methoxy-phenyl amine	Cyclo Hexane carbaldeh yde	6-Chloro-4-cyclohexyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	CRX 001113	ESI(+) = 372
4-Isopropyl -phenyl amine	2,4-Dichloro-benz aldehyde	4-(2,4-Dichloro-phenyl)-8-isopropyl -3a,4,5,9b-	CRX 001114	ESI(+) = 358

		tetrahydro-3H-cyclopenta [c]quinoline		
1-(4-Amino-phenyl)-2,2,2-trifluoro-ethanone	2,4-Dichloro-benz aldehyde	1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9 b-tetrahydro-3H-cyclopenta[c] quinolin-8-yl]-2,2,2-trifluoro-ethanone	CRX 001085	^{1}H NMR (DMSO) δ=1.5 (m, 1H), 1.2 (m, 1H), 3.0 (q, 1H), 4.0 (d, 1H)5.0 (d, 1H), 5.5 (d, 1H), 5.9 (bs, 1H), 6.7 (d, 1H), 7.3 (s, 1H), 7.4-7.6 (m, 5H)
4-Amino-benzamide	2,4-Dichloro-benz aldehyde	4-(2,4-Dichloro-phenyl)-3a,4,5,9b-t etrahydro-3H-cyclopenta[c] quinoline -8-carboxylic acid amide	CRX 000760	APCI(+)=359

Example 2.3 Preparation of 4-(2,4-dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-ylamine(CRX 000765)



First step: The aldehyde (294 mg, 1.68 mmol, 1 eq.) was added to a solution of aniline (350 mg, 1.68 mmol, 1 eq.) and $MgSO_4$ (420 mg, 3.36 mmol, 2 eq.) in 10 mL of toluene. The reaction mixture was stirred at 25°C for 12h, and the solvents were evaporated to give the imine(85%).

Second step: TFA (98 µL, 1.28 mmol, 0.9 eq.) was added to a solution of imine (519 mg, 1.42 mmol, 1 eq.) in 20 ml of acetonitrile. After 10 min, cyclopentadiene (1.07 mL, 5.68 mmol, 4 eq.) was added. The reaction mixture was stirred at 25°Ct for 12h. The solution was washed with $NaHCO_3$ saturated and extracted with ether. The organic layers were combined, dried over Na_2SO_4, filtered and the solvent evaporated. The residue was purified by flash chromatography (EtOAc/Hexane 2:8) to afford the product (80%).

The compound prepared in the first step (described above) (430 mg, 1.55 mmol, 1 eq.) was dissolved in 20 mL CH_2Cl_2, 2 mL of TFA and 0.17 mL of anisole (1.55 mmol, 1 eq.) and the resulting solution stirred during 5h. The solvents were evaporated and the residue triturated with ether and ethanol. The precipitate was filtered to give the product as a white solid (36%).

^{1}H NMR ($CDCl_3$) δ= 1.6 (m, 1H), 2.4 (m, 1H), 3.1 (qd, 1H), 4.0 (d, 1H), 4.7 (d, 1H), 5.6 (d, 1H), 5.7 (bs, 1H), 5.9 (s, 1H), 6.7 (d, 1H), 6.8 (d, 1H), 6.9 (s, 1H), 7.5 (d, 1H), 7.7 (m, 2H), 9.4 (bs, 2H)

Example 2.4 The following compounds were obtained after reduction on Pd/C with hydrogen in methanol of the insaturated intermediates.

Amine	Aldehyde	Cyclopenta (c) quinoline (compound of Formula I)	CRX number
4-Trifluoromethoxy-phenylamine	4-Amino-benzaldehyde	4-(8-Trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinolin-4-yl)-phenylamine	CRX000372
4-Trifluoromethoxy-phenylamine	3-Amino-benzaldehyde	3-(8-Trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinolin-4-yl)-phenylamine	CRX000373
1-(4-Amino-phenyl)-ethanone	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline	CRX000479
4-Trifluoromethoxy-phenylamine	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline	CRX000480
4-Trifluoromethoxy-	Naphthalene-1-	4-Naphthalen-1-yl-8-	CRX000481

phenylamine	carbaldehyde	trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline	
4-Trifluoromethyl-phenylamine	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-8-trifluoromethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline	CRX000483
4-Trifluoromethoxy-phenylamine	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline	CRX000425
1-(4-Amino-phenyl)-ethanone	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline	CRX000484
4-Trifluoromethyl-phenylamine	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-8-trifluoromethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline	CRX000502
4-Amino-benzoic acid ethyl ester	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline-8-carboxylic acid ethyl ester	CRX000499
4-Amino-benzoic acid ethyl ester	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline-8-carboxylic acid ethyl ester	CRX000500
4-Trifluoromethoxy-	2-Amino-benzaldehyde	2-(8-Trifluoromethoxy	CRX000565

phenylamine		-2,3,3a,4,5,9b -hexahydro-1H- cyclopenta[c] quinolin-4-yl)- phenylamine	
4- Trifluoromethoxy- phenylamine	2-Chloro-4- fluoro- benzaldehyde	4-(2-Chloro-4- fluoro-phenyl)- 8- trifluoromethoxy -2,3,3a,4,5,9b- hexahydro-1H- cyclopenta[c] quinoline	CRX000592
4- Trifluoromethoxy- phenylamine	Biphenyl-4- carbaldehyde	4-Biphenyl-4-yl- 8- trifluoromethoxy -2,3,3a,4,5,9b- hexahydro-1H- cyclopenta[c] quinoline	CRX000594
4- Trifluoromethoxy- phenylamine	2-Methoxy- benzaldehyde	4-(2-Methoxy- phenyl)-8- trifluoromethoxy -2,3,3a,4,5,9b- hexahydro-1H- cyclopenta[c] quinoline	CRX000597
4- Trifluoromethoxy	2-Chloro- benzaldehyde	4-(2-Chloro- phenyl)-8- trifluoromethoxy -2,3,3a,4,5,9b- hexahydro-1H- cyclopenta[c] quinoline	CRX000598
4- Trifluoromethoxy	4-Chloro- benzaldehyde	4-(4-Chloro- phenyl)-8- trifluoromethoxy -2,3,3a,4,5,9b- hexahydro-1H- cyclopenta[c] quinoline	CRX000599

Example 2.5 Similarly, the following compounds were obtained by the same protocol:

Amine	Aldehyde	Cyclopenta (c) quinoline (compound of Formula I)	CRX number	Analysis
2-(4-Amino-phenyl)-1,1,1,3,3,3-hexa fluoro-propan-2-ol	2,4-Dichloro-benzaldehyde	2-[4-(2,4-Dichloro-phenyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol	CRX000927	APCI(+) =484
4-Trifluoro methoxy-phenylamine	Formaldehyde	2,2,2-Trifluoro-1-(8-trifluoro methoxy-1,2,3,3a,4,9b-hexahydro-cyclopen ta[c] quinolin-5-yl)-ethanone	CRX000953	Mp = 62°C
4-Trifluoro methoxy-phenylamine	Formaldehyde	8-Trifluoro methoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline	CRX000961	APCI(+) =258
2-(4-Amino-phenyl)-1,1,1,3,3,3-hexafluoro-propan-2-ol	4-Fluoro-2-trifluoro methyl-benzaldehyde	1,1,1,3,3,3-Hexafluoro-2-[4-(4-fluoro-2-trifluoro methyl-phenyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]	CRX000966	ESI(+) = 502

		quinolin-8-yl]-propan-2-ol		
4-Trifluoromethyl-phenylamine	Cyclohexane carbaldehyde	4-Cyclohexyl-8-trifluoro methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline	CRX000990	APCI(+) =324
4-Trifluoro methyl-phenylamine	4-Fluoro-2-trifluoro methyl-benzaldehyde	4-(4-Fluoro-2-trifluoro methyl-phenyl)-8-trifluoro methyl-2,3,3a,4,5,9b-hexahydro-4-Trifluoro methyl-phenylamine 1H-cyclopenta[c] quinoline	CRX001016	APCI(+) =404

All the above listed cyclopenta[c]quinolines are compounds of Formula (I), and are either used as active compounds according to the present invention, or as synthetic intermediates for obtaining cyclopenta[c]quinoline derivates of Formula (I).

Example 3 : Synthesis of 4-(2,4-dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX156651).

4-Trifluoromethoxy-phenylamine (910 mg, 5.1 mmol) is dissolved in CH_3CN (10 ml). TFA (0,36 ml, 4.6 mmol) is added, under argon atmosphere and at room temperature. After 15 min, a CH_3CN solution of freshly distillated cyclopentadiene (14 g of cyclopentadiene in 39 ml of CH_3CN, 5.5 ml, 4 eq) is added. Finally, 2,4-dichlorobenzaldehyde (900 mg, 5.1 mmol) is added. The mixture is stirred at room temperature for 48h.

The solvent is removed under vacuum. The residue is dissolved in ethyl acetate and washed with a saturated aqueous solution of $NaHCO_3$. After usual workup the crude product is purified by column chromatography with heptane/ethyl acetate 7/3 as eluent to obtain 4-(2,4-dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline as a white off solid (1.37 g, 70%).

Analytical data :

$C_{19}H_{14}Cl_2F_3NO$

MM : 400,23 g/mol

MS (ESI+) : 399

RMN ^1H (400 MHz, $CDCl_3$) δ (ppm) : 1.76-1.82 (m, 1H), 2.55-2.59 (m, 1H), 3.21-3.25 (m, 1H), 3.62 (broad s, 1H), 4.13 (d, 1H, 12 Hz), 4.97 (thin m, 1H), 5.68 (m, 1H), 5.82 (m, 1H), 6.59-7.60 (m, 6H).

Example 4 : Saponification of cyclopenta[c]quinoline esters to obtain cyclopenta[c]quinoline acids of the invention.

The cyclopenta[c]quinoline esters described in Example 2 have been further modified in order to obtain compounds of formula (I) under the acid form.

An aqueous solution of 6M LiOH or NaOH or KOH (4 eq) is added to a solution of cyclopenta[c]quinoline ester (1 eq) in THF. The mixture is stirred at room temperature for 4 h, with heating if necessary. The THF is then evaporated and the aqueous residue solution cooled at 0°C. The mixture is acidified to pH 2 with drop wise addition of concentrated HCl. The precipitate is filtered, washed with water and dried under vacuum.

This general protocol has been used for preparing the following compounds of the invention :

cyclopenta[c]quinoline ester	cyclopenta[c]quinoline acids of the invention	CRX number
4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline -8-carboxylic acid	CRX123477
4-(4-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	4-(4-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid	CRX101004
4-(3-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	4-(3-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid	CRX156678
4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid	
4-(2-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid ethyl ester	4-(2-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid	CRX156679
4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline -8-carboxylic acid ethyl ester	4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline -8-carboxylic acid	
4-(4-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid ethyl ester	4-(4-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid	
4-(2,3-Dichloro-phenyl)-2,3,3a,4,5, 9b-hexahydro-1H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester	4-(2,3-Dichloro-phenyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline-8-carboxylic acid	CRX 000501
8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid ethyl ester	8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid	CRX000762

Example 5 : Synthesis of 4-(2,3-dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid (CRX123477)

4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester, named CRX123485, (300 mg, 0.8 mmol) is dissolved in THF/water : 1/1 (40 ml). A solution of 6M NaOH (0.5 ml, 4eq) is added. The mixture is stirred at room temperature for 4h. THF is then evaporated and the residue solution is cooled to 0°C. By addition of concentrated HCl, a precipitate is formed. It is filtered, washed with water and dried under vacuum to obtain 4-(2,3-dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid as a white solid (260 mg, 90%).

Analytical data :

$C_{19}H_{15}Cl_2NO_2$

MM : 360.24 g/mol

MS (ESI+) : 359

RMN ^1H (400 MHz, $CDCl_3$) δ (ppm) : 1.70-1.76 (m, 1H), 2.45-2.55 (m, 1H), 3.22-3.30 (m, 1H), 3.95 (large s, 1H), 4.15 (d, 1H, 12 Hz), 5.12 (thin m, 1H), 5.61 (m, 1H), 5.90 (m, 1H), 6.60-7.80 (m, 6H).

Example 6 : Formation of the amide derivatives of cyclopenta[c]quinoline .

6.1. Formation of the cyclopenta[c]quinoline acid chloride intermediate.

The cyclopenta[c]quinoline acids of example 4 are used as starting material. The selected cyclopenta[c]quinoline acid, in anhydrous toluene, is mixed with thionyl chloride and 3-4 drops of dimethylformamide. The mixture is heated to 110°C for 2h. The excess of thionyl chloride and solvents are

removed under vacuum and the crude product is triturated with hexane and used without further purification.

6.2. Formation of the amide derivatives of cyclopenta[c]quinoline.

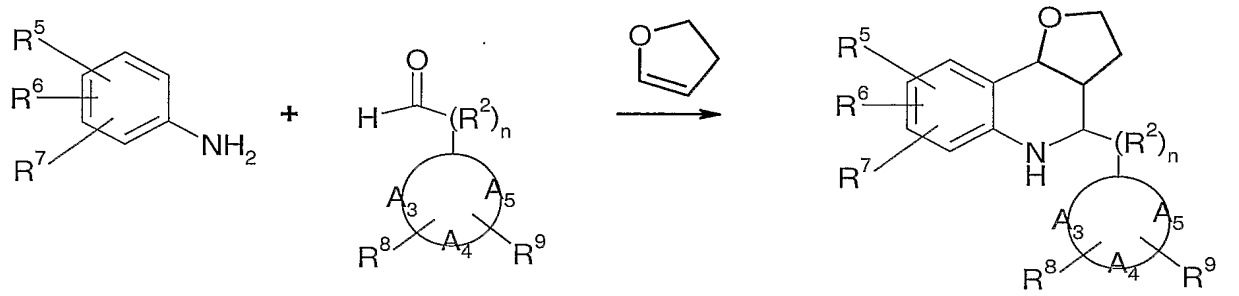
Triethylamine (2 eq) is added to a solution of cyclopenta[c]quinoline acid chloride intermediate (see 5.1, 1 eq) in dry dimethylformamide, under argon atmosphere, at room temperature. The desired amine is then added drop wise. The mixture is stirred at room temperature for 4h. The solution is heated at 60°C if necessary. Solvents are then evaporated and after usual workup, the crude product is purified from the appropriate solvent either by colomn chromatography or by recrystallisation.

This general protocol has been used for preparing the following compounds of the invention :

acid intermediates	amide derivatives of the invention	CRX numbers
4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid	4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid diethylamide	CRX156773
4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid	4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid diethylamide	CRX156766
4-(4-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid	4-(4-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid diethylamide	CRX156778
4-(4-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid	[4-(4-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-6-yl]-morpholin-4-yl-methanone	CRX156676

Example 7 : Synthesis of hexahydro-furo[3,2-c]quinoline of the invention (Crousse et al., 2000, J. Org. Chem. , 65, 5009-5013)

Scheme 2 : general synthesis protocol



Amine **Aldehyde** **Hexahydro-furo-quinoline**

BF_3 Et_2O (0,1 eq) is added to a solution of amine (1 eq) and aldehyde (1 eq) in dry toluene, at -78°C. After stirring for 10 min, 2,3-dihydrofuran (1,7 eq) in dry toluene is added. The reaction mixture is stirred for 30 min. Then saturated aqueous $NaHCO_3$ is added, and the product is extracted with ether. After usual workup, the crude product is purified by chromatography on silica gel.

Said general protocol has been used for preparing the following compounds of the invention :

Aniline	Aldehyde	hexahydro-furo[3,2-c]quinoline	CRX number
4-Methoxy-phenylamine	Furan-2-carbaldehyde	4-Furan-2-yl-8-methoxy-2,3,3a,4,5,9b-hexahydro-furo[3,2c]quinoline	CRX156680
Aniline	Benzaldehyde	4-Phenyl-2,3,3a,4,5,9b-hexahydro-furo[3,2c]quinoline	CRX156681

4-Methyl-phenylamine	Furan-2-carbaldehyde	4-Furan-2-yl-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2c]quinoline	CRX156682
4-Methyl-phenylamine	4-Chloro-benzaldehyde	4-(4-Chloro-phenyl)-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000435
4-Methyl-phenylamine	2-Chloro-benzaldehyde	4-(2-Chloro-phenyl)-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000436
4-Methyl-phenylamine	Benzaldehyde	8-Methyl-4-phenyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000437
4-Methoxy-phenylamine	2-Furaldehyde	4-Furan-2-yl-8-methoxy-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000482
4-Methyl-phenylamine	3-Furaldehyde	4-Furan-3-yl-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000485
4-Methyl-phenylamine	2,3-Dimethoxy-benzaldehyde	4-(2,3-Dimethoxy-phenyl)-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000490
4-Methyl-phenylamine	2,3-Dichloro-benzaldehyde	4-(2,3-Dichloro-phenyl)-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000495
4-Methyl-phenylamine	3-Chloro-benzaldehyde	4-(3-Chloro-phenyl)-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000496
4-Methyl-phenylamine	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000497
4-Methyl-phenylamine	Pyridine-3-carbaldehyde	8-Methyl-4-pyridin-3-yl-2,3,3a,4,5,9b-	CRX 000498

		hexahydro-furo[3,2-c]quinoline	
4-Trifluoromethoxy-phenylamine	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000526
4-Trifluoromethyl-phenylamine	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-8-trifluoromethyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000527
4-Methyl-phenylamine	2,6-Dichloro-benzaldehyde	4-(2,6-Dichloro-phenyl)-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000528
4-Methyl-phenylamine	2,4-Dichloro-benzaldehyde	4-(2,4-Dichloro-phenyl)-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000529
4-Methyl-phenylamine	2-Furaldehyde	4-Furan-2-yl-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000530
4-Methyl-phenylamine	3-Chloro-benzaldehyde	4-(3-Chloro-phenyl)-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX 000531

Aniline	**Aldehyde**	**hexahydro-furo[3,2-c]quinoline**	**CRX number**	**Analysis**
4-Trifluoro methoxy-phenyl amine	Furan-2-carbaldehyde	4-Furan-2-yl-8-trifluoro methoxy-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX000385	Mp = 86°C
p-Tolylamine	Oxo-acetic acid ethyl ester	8-Methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-	CRX000489	Mp = 77°C

		c]quinoline-4-carboxylic acid ethyl ester		
p-Tolylamine	Furan-2-carbaldehyde	4-Furan-2-yl-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline	CRX000488	APCI(+)= 256

Example 8. CRX15651 induces complex between 6xHis LXR alpha LBD protein and the co-activator derived peptide SRC3n3

In order to test the ability of CRX156651 to induce the formation of nuclear receptor/co-activator complex, the amplified luminescent proximity homogenous assay (Alphascreen™) was used (Ullman, et al., 1994, Proc Natl Acad Sci U S A. 91, 5426-5430). In this assay, a streptavidine coated donor bead and a Ni^{2+} coated acceptor bead are brought into proximity by a bimolecular interaction of binding partners immobilized to these beads. Excitation of the assay mixture with a high-intensity laser at 680 nm induces the formation of singlet oxygen at the surface of the donor bead, following conversion of ambient oxygen to a more excited singlet state by a photosensitizer present in the donor bead. The singlet oxygen molecules can diffuse up to 200 nm, and, if an acceptor bead is in proximity, can react with a thioxene derivative present in this bead, generating chemiluminescence at 370 nm that further activates the fluorophores contained in the same bead. The fluorophores subsequently emit light at 520-620 nm.

Alphascreen™ was performed in 384 wells plate in total volume of 25 ul of reaction buffer composed of 50 mM TRIS pH 8.0, 50 mM KCl, 1 mM DTT, 0.1% BSA. The purified 6xHis LXR alpha LBD protein (2 nM) was coupled to the 20 ug/ml of Ni^{2+} coated acceptor beads (Perkin Elmer) in the presence of 4 uM

CRX156651 or its absence, for 30 min at room temperature in dark. Following coupling, streptavidine coated donor beads (Perkin Elmer) and biotinylated SCR3 nuclear box 3 peptide (Neosystem) were added to the final concentration of 20 ug/ml and 50 nM, respectively. The mix was incubated for an additional 60 min at room temperature in dark and chemiluminiscence was read using Fusion, PerkinElmer. The positive signal cut off corresponded to the three fold of standard error deviation of each experiment in the absence of compound.

Example 9. CRX156651 activates human LXR alpha and is a partial agonist

The CV1 cell lines were obtained from ATCC (Rockville, MD). Cells were maintained in Dulbecco's modified Eagle's minimal essential medium (DMEM) supplemented with 10 % foetal calf serum (FCS), L-glutamine (2 mM), and antibiotics (penicillin/streptomycin). In order to test the ability of CRX156651 to activate human LXR alpha, CV1 cells (2.5×10^4 cells per well of a 96 wells plate) were grown at 37°C under a 5% CO_2 atmosphere in DMEM medium supplemented with 10% lipid deficient serum.

Cotransfection was performed by adding in each well 0.2 ng of hLXR alpha plasmid, 8 ng of the luciferase reporter plasmid, 8 ng of pCMV-betaGAL plasmid and 72 ng of a carrier plasmid (pBluescript, Statagene) which allows increasing amount of total transfected DNA in order to improve transfection efficiency. Said co-transfection is realised using the FuGENE 6 transfection reagent (Roche) according to the manufacturer's instructions.

After about 16 hours of growth, the medium was changed by fresh supplemented DMEM. Cells were treated with increasing doses (from 1.10^{-10} to 1.10^{-5} M, see Figure 1) of

T0901317 or compound CRX156651 and incubated for 24 hours as mentioned above.

Cells were lysed with 100 ul of lysis buffer (40 mM TRIS pH 7.8, 2.14 mM $MgCl_2$, 5.4 mM $MgSO_4$, 0.2 mM EDTA, and 66.6 mM DTT). 50 ul of the lysate were subjected to luciferase assay, whereas 30 ul of lysate were used for beta-galactosidase assay. The luciferase data were normalised to beta-galactosidase activity and data are presented in RLU (Relative Light Unit). The EC50 were calculated using Graphpad Prism.

Figure 1 shows that CRX156651 is an agonist of human LXR alpha: it activates in a dose dependent manner the expression of luciferase gene. CRX156651 shows good potency since the calculated EC50 is 305 nM, which is only 15 times higher that the one observed for T0901317 (20 nM). The efficacy is thus about 60% of the one observed with T0901317. Accordingly, we can conclude that said compound has partial agonist property.

Similar experiments have been conducted with other compounds of the Invention. The obtained results are presented below :

CRX number	EC50	Vmax
CRX 000412	251	47
CRX 123477	280	16
CRX 000292	300	17
CRX 000369	333	55
CRX 000425	115	41
CRX 000481	297	63
CRX 000480	233	36
CRX 000502	130	57
CRX 000500	720	54
CRX 000483	199	27

CRX 000479	612	21
CRX 000484	651	29

Example 10. CRX156651 activates gene implicated in cholesterol efflux

The THP-1 cells were obtained from ATCC (Rockville, MD). Cells were maintained in RPMI 1640 medium (GIBCO) supplemented with 10 % foetal bovine serum, sodium pyruvate (1 mM), HEPES (10 mM), beta-mercapto-ethanol (0.05 mM), L-glutamine (2 mM) and antibiotics (penicillin/streptomycin). In order to test the ability of said compound to activate gene implicated in cholesterol efflux, the ABCA1 gene, the THP-1 cells (2.5 x 10^4 cells per well of a 96 wells plate) were differentiated at 37°C under a 5% CO_2 atmosphere in RPMI medium supplemented with 0.2 uM phorbol 12-myristate-13-acetate (SIGMA). The medium was change every third day.

After 5 days of differentiation, the medium was changed by fresh RPMI medium supplemented with 10% lipid deficient medium. Cells were treated with increasing doses (from 1.10^{-10} to 1.10^{-5} M, see Figure 2) of GW3965 or compound CRX156651 and incubated for 24 hours as mentioned above.

Real time quantitative PCR was used to determine the relative levels of ABCA1 mRNA. Total RNAs were isolated using the SV Total RNA Isolation System (Promega) according to the instructions from the manufacturer. RNAs were converted to a single stranded cDNA with the Reverse Transcription system (AMV, Promega) and random primers following the recommendations of the manufacturer, in a 96 wells plate in a thermocycler at 42 °C for 1 hour. RNA levels were measured by quantitative PCR using the LightCycler-FastStart DNA SYBRGreen I™ kit (Roche Diagnostics) on the LightCycler™ system (Roche Diagnostics). Primers (5′-TGTCCAGTCCAGTAATGGTTCTGTGT-3′ and 5′-GCGAGATATGGTCCGGATTG-3′)

were as described in Oliver *et al.* (Oliver, et al., 2001, Proc. Natl. Acad. Sci., 98, 5306-5311). 40 PCR cycles were performed essentially as described by the manufacturer with 2 µl of cDNA in the presence of 0.4 µM of each primer, 3 mM $MgCl_2$ with an annealing at 60 °C and extension at 72 °C for 19 seconds. The specificity of the fluorescence signal was verified by a melting curve analysis at the end of the run. The quantification was performed based on the CP determination obtained via the Second Derivative Maximum Method from the LightCycler™. The relative expression ratio of the target gene in a sample X compared to a calibrator or control sample is described by the equation : $Ratio=E^{-CPx-CPcont}$ (Pfaffl, et al., 2002, Nucleic Acids Res. 30, 36); with E representing the PCR efficiency for each pair of primers. Samples were analysed in duplicate or triplicate in 3 independent experiments.

Figure 2 shows that CRX156651 activates the ABCA1 gene expression in a dose dependent manner. CRX156651 shows efficacious dose (ED50) in the ABCA1 functional test of 2870nM to compare with the EC50 305 nM obtained in transient transfection assays. The efficacy is about 63% of the one observed with full agonist, the GW3965.

Example 11. CRX156651 activates differentially gene implicated in lipogenesis and thus separates cholesterol efflux from lipogenesis

The HepG2 cells were obtained from ATCC (Rockville, MD). Cells were maintained in MEM medium (GIBCO) supplemented with 10 % foetal bovine serum, non essential amino acids (0.1 mM), sodium pyruvate (1 mM), L-glutamine (2 mM) and antibiotics (penicillin/streptomycin). In order to test the ability of CRX156651 to activate genes implicated in lipogenesis, fatty acid synthase (FAS) and sterol response element binding protein 1c (SREBP1c), the HepG2 cells (2.5 x 10^4 cells per

well of a 96 wells plate) were grown at 37°C under a 5% CO_2 atmosphere in MEM medium supplemented with 10% lipid deficient serum.

After 24 hours, the medium was changed by fresh medium supplemented with 10% lipid deficient medium. Cells were treated with increasing doses (from 1.10^{-10} to 1.10^{-5} M, see Figure 3) of GW3965 or compound CRX156651 and incubated for 24 hours as mentioned above.

Real time quantitative PCR was used to determine the relative levels of FAS mRNA. Total RNAs were isolated by using the SV Total RNA Isolation System (Promega) according to the instructions from the manufacturer. RNAs were converted to a single stranded cDNA with the Reverse Transcription system (AMV, Promega) and random primers following the recommendations of the manufacturer, in a 96 wells plate in a thermocycler at 42°C for 1 hour. RNA levels were measured by quantitative PCR using the LightCycler-FastStart DNA SYBRGreen I kit (Roche Diagnostics) on the LightCycler system (Roche Diagnostics). Oligonucleotide primers 5′-GGTGTTTGTCTGTGTTTGTTTTTCA-3′ and 5′-AGATCACATGCGGTTTAATTGTGG-3′ for FAS and 5′-GCGGAGCCATGGATTGCAC-3′ and 5′-CTCTTCCTTGATACCAGGCCC-3′ for SREBP1c, respectively were designed using the Probe Design program (Roche Diagnostics) and synthetised by Genset. 40 PCR cycles were performed essentially as described by the manufacturer with 2 μl of cDNA (1/10 dilution for FAS) in the presence of 0.4 μM of each primer, 3 mM $MgCl_2$ and annealing at 60 °C and extension at 72 °C for 19 seconds. The specificity of the fluorescence signal was verified by a melting curve analysis at the end of the run. The quantification was performed based on the CP determination obtained via the Second Derivative Maximum Method from the LightCycler. The relative expression ratio of the target gene in a sample X compared to a calibrator or control sample is

described by the equation: $Ratio=E^{-CPx-CPcont}$ (Pfaffl, et al., 2002, Nucleic Acids Res. 30, 36); with E representing the PCR efficiency for each pair of primers. Samples were analysed in duplicate or triplicate in 3 independent experiments.

Figures 3A and 3B show that CRX156651 activates the FAS and SREBP1c gene expression in a dose dependent. The efficacy is about 39% and 31% of GW3965 for FAS and SREBP1c, respectively. The efficacious dose (ED50) of CRX156651 is 593nM in the FAS functional test and 377 nM in the SREBP1c functional test.

Example 12. CRX156651 activates differentially gene regulating plasma triglyceride levels

The HepG2 cells were obtained from ATCC (Rockville, MD). Cells were maintained in MEM medium (GIBCO) supplemented with 10 % foetal bovine serum, non essential amino acids (0.1 mM), sodium pyruvate (1 mM), L-glutamine (2 mM) and antibiotics (penicillin/streptomycin). In order to test the ability of CRX156651 to activate a gene regulating plasma triglyceride levels angiopoietin-like protein 3 (Angptl3), the HepG2 cells (2.5×10^4 cells per well of a 96 wells plate) were grown at 37°C under a 5% CO_2 atmosphere in MEM medium supplemented with 10% lipid deficient serum.

After 24 hours, the medium was changed by fresh medium supplemented with 10% lipid deficient medium. Cells were treated with increasing doses (from 1.10^{-10} to 1.10^{-5} M, see Figure 4) of GW3965 or compound CRX156651, and incubated for 24 hours as mentioned above.

Real time quantitative PCR was used to determine the relative levels of Angptl3 mRNA. Total RNAs were isolated by using the SV Total RNA Isolation System (Promega) according to the instructions from the manufacturer. RNAs were converted to a single stranded cDNA with the Reverse Transcription system (AMV, Promega) and random primers

following the recommendations of the manufacturer, in a 96 wells plate in a thermocycler at 42°C for 1 hour. RNA levels were measured by quantitative PCR using the LightCycler-FastStart™ DNA SYBRGreen I kit (Roche Diagnostics) on the LightCycler™ system (Roche Diagnostics). Oligonucleotides primers 5′-TCAATGAAACGTGGGAGA-3′ and 5′-TTGCCAGTAATCGCAAC-3′ were designed using the Probe Design program (Roche Diagnostics) and synthesized by Genset. 40 PCR cycles were performed essentially as described by the manufacturer with 2µl of cDNA in the presence of 0.4 µM of each primer, 3 mM $MgCl_2$ and annealing at 58 °C and extension at 72 °C for 19 seconds. The specificity of the fluorescence signal was verified by a melting curve analysis at the end of the run. The quantification was performed based on the CP determination obtained via the Second Derivative Maximum Method from the LightCycler™. The relative expression ratio of the target gene in a sample X compared to a calibrator or control sample is described by the equation: $Ratio=E^{-CPx-CPcont}$ (Pfaffl, et al., 2002, Nucleic Acids Res. 30, 36); with E representing the PCR efficiency for each pair of primers. Samples were analysed in duplicate in 3 independent experiments.

Figure 4 shows that CRX156651 activates the Angptl3 gene expression in a dose dependent manner but to the significantly lower extent than GW3965 does. The efficacy is about 44 % of GW3965 and the efficacious dose (ED50) of CRX156651 in the Angptl3 functional test is 7507nM.

Example 13. CRX156651 promotes cholesterol efflux *in vitro*.

The THP-1 cells were obtained from ATCC (Rockville, MD). Cells were maintained in RPMI 1640 medium (GIBCO) supplemented with 10 % foetal bovine serum, sodium pyruvate (1 mM), HEPES (10 mM), beta-mercapto-ethanol (0.05 mM), L-

glutamine (2 mM) and antibiotics (penicillin/streptomycin). In order to test the ability of said compound to stimulate cholesterol efflux, the THP-1 cells (1.5 x 10^5 cells per well of a 48 wells plate) were differentiated at 37°C under a 5% CO_2 atmosphere in RPMI medium supplemented with 0.2 uM phorbol 12-myristate-13-acetate (SIGMA). The medium was change every third day.

After 5 days of differentiation, the cells were loaded for 24 h with 50ug/ml acetylated LDL (Intracel) and 1 uCi/ml [^{3}H] cholesterol (Amersham) in the medium supplemented with 10% lipid deficient medium. Cells were washed twice with phosphate saline buffer and equilibrated in RPMI 1640 medium (GIBCO) supplemented with 0.2 % bovine serum albumin, sodium pyruvate (1 mM), HEPES (10 mM), beta-mercapto-ethanol (0.05 mM), L-glutamine (2 mM) and antibiotics (penicillin/streptomycin) for 4 hours. Cells were washed with phosphate saline buffer and then treated with the said compound at final concentration 3uM for 16 h with or without 15 ug/ml ApoAI (Intracel). Medium was collected and centrifuged at 14,000 rpm for 2 min to remove debris. Cholesterol was extracted with 250 ul of isopropanol. Scintillation counts were taken of medium and cells. The percentage of efflux was determined for each well using the formula: counts media/(counts cells +counts media)*100. The experiment was performed in quadruplicate.

Figure 5 shows that CRX156651 stimulates the ApoAI specific cholesterol efflux to the similar extent as GW3965 does. The efficacy is about 72% of GW3965.

Example 14. CRX156651 improves plasma lipid profile *in vivo*

C57BL/6 mice were obtained from Charles Rivers and fed *ad libitum* a normal chow diet (DO3, UAR). Experiment was performed on 8 weeks old male mice. The said compound at

dose of 10 mg/kg was orally administered daily in 0.5% methylcellulose for 7 days. Body weight and food intake were monitored daily.

Mice were fasted for 3 hours following the last gavage. Blood was collected by retro-orbital punction. HDL levels were determined using commercially available enzymatic kit (Olympus System Reagent, Olympus Diagnostica GmbH). Comparisons between control and treated mice were made by using the Student *t* test.

Figure 6 shows that CRX156651 has beneficial effect on the HDL-cholesterol levels following 7 days administration to C57BL/6 mice.

Example 15. CRX156651 does not increase plasma and liver triglyceride levels *in vivo*

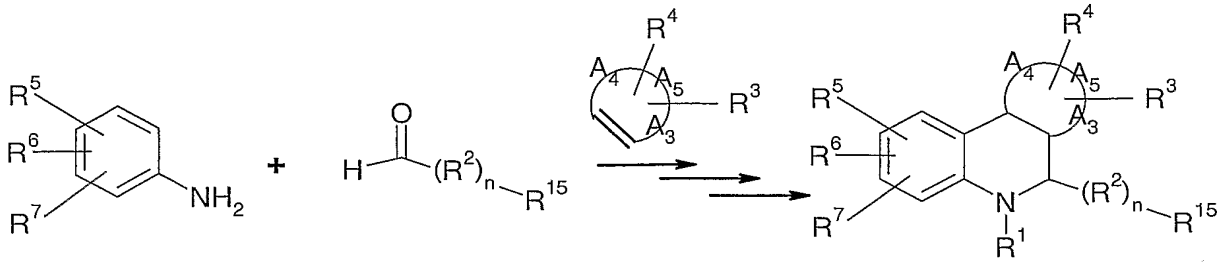
C57BL/6 mice were obtained from Charles Rivers and fed *ad libitum* a normal chow diet (DO3, UAR). Experiment was performed on 8 weeks old male mice. The said compound at dose of 10 mg/kg was orally administered daily in 0.5% methylcellulose for 7 days. Body weight and food intake were monitored daily.

Mice were fasted for 3 hours following the last gavage. Blood was collected by retro-orbital punction and plasma triglyceride levels were determined using commercially available enzymatic kit (Olympus System Reagent, Olympus Diagnostica GmbH). Liver triglycerides were extracted by Folch method and determined by TG PAP 1000 Biomerieux reagent. Comparisons between control and treated mice were made by using the Student *t* test.

Figure 7A / 7B shows that CRX156651 does not increase the plasma and liver triglyceride levels, respectively.

Example 16. Synthesis of compounds of general formula (II).

General Reaction Scheme :



Amine Aldehyde formula (I)

Tetrahydroquinolines of formula (I) are obtained by an imino Diels-Alder reaction (Buonora and Olsen, 2001, Tetrahedron, 57, 6099-6138) such as described in the reaction scheme above.

This three components reaction is set with amines, aldehydes and appropriate dienophiles in suitable solvents, such as acetonitrile, dichloromethane, ether, THF, toluene, fluorinated alcohols, with acidic catalysis, such as TFA or Lewis Acid catalysts (chiral or not) and with heating where necessary (Spanedda et al., 2003, Tetrahedron Letters, 44, 217-219 ; Sundararajan et al., 2001, Organic Letters, 3, 1973-1976 ; Hadden et Stevenson, 1999, Tetrahedron Letters, 40 , 1215-1218 ; Babu et Perumal, 1998, Tetrahedron Letters, 39, 3225-3228).

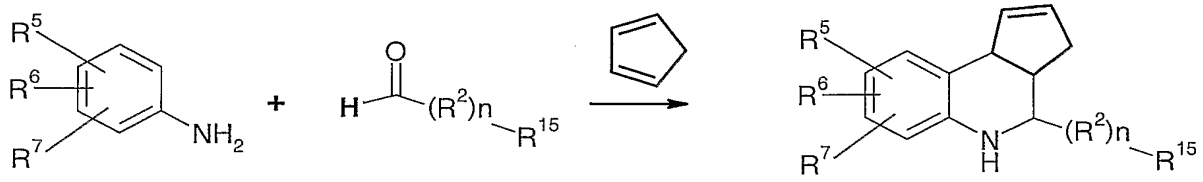
Introduction of the R_1 group on the nitrogen is made according to methods known to those skilled in the art e.g. alkylation with methyl iodide in the presence of a base.

If, in any of the other processes mentioned herein, the substituting moiety R^1, R^2, R^3, R^4, R^5, R^6 and/or R^7 is different from the one required, the substituting moiety may be converted to the desired moiety by known methods. The substituting moiety R^1, R^2, R^3, R^4, R^5, R^6 and/or R^7 may also need protection against the conditions under which reactions are carried out, accordingly, a protecting group may be used which is removed after reactions have been completed.

The individual isomers of [I] may be separated using, for example, column chromatography, HPLC or recrystallisation.

Example 16.1 : Synthesis of cyclopenta[c]quinoline of the invention (WO98/27427)

Scheme 1 : general synthesis protocol



Amine Aldehyde cyclopenta[c]quinoline

TFA (0.9 eq) is added drop wise to a solution of amine (R5, R6, R7-phenyl amine) (1 eq) in CH_3CN. Freshly distillated cyclopentadiene (4 eq), dissolved in CH_3CN, is then added. Finally, the aldehyde (1 eq) is added drop wise. The mixture is stirred at room temperature for 4 to 48 hours. The solvent is then removed under vacuum. The residue is dissolved in ethyl acetate and washed with a saturated aqueous solution of $NaHCO_3$. The crude product is purified by column chromatography with heptane/ethyl acetate (7/3) or heptane/methylene chloride (6/4) as eluent to afford the compound.

This protocol was used for preparing the compound of the invention 9-Chloro-6-trifluoromethyl-a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid isopropyl ester.

Example 16.2: Saponification of cyclopenta[c]quinoline ester to cyclopenta[c]quinoline acid :

The general synthetic protocol is as follows:

An aqueous solution of 6M LiOH or NaOH or KOH (4 eq) is added to a solution of a desired cyclopenta[c]quinoline ester (1 eq) in THF. The mixture is stirred at room temperature for

4 h, with heating if necessary. Then, the THF is evaporated and the aqueous residue solution is cooled at 0°C. The mixture is acidified to pH 2 with drop wise addition of concentrated HCl. The precipitate is filtered, washed with water and dried under vacuum.

This protocol was used for preparing the compound of the invention 9-Chloro-6-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid, named CRX156767.

Example 17. Reduction of cyclopenta[c]quinoline esters or ketones to obtain cyclopenta[c]quinoline alcools of the invention.

The compounds of the invention listed below have been obtained by classical reduction with $LiAlH_4$ (Aicher and Kishi, 1987, Tetrahedron Letters, 28, 3463-3466).

Esters or Ketones intermediates	alcool derivatives of the invention	CRX numbers	Analysis
4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline -8-carboxylic acid ethyl ester	[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin -8-yl]-methanol	CRX000896	ESI(+) =346
1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9 b-tetrahydro-3H-cyclopenta[c] quinolin-8-yl]-ethanone	1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin-8-yl]-ethanol	CRX000906	ESI(+) =360
1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9 b-tetrahydro-3H-cyclopenta[c] quinolin-8-yl]-2,2,2-trifluoro-ethanone	1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9 b-tetrahydro-3H-cyclopenta[c] quinolin-8-yl]-2,2,2-trifluoro-ethanol	CRX001116	ESI(+) =414

Example 18. Functionalisation of C-THQ

The following compounds were obtained by well known reactions of peptide coupling with EDCI-DMAP (Desai et Stramiello, 1993, Tetrahedron Letters, 34, 7685-7688) or alkylation with $CsCO_3$ or Et_3N (Lowden et al., 2003, J. Med. Chem., 46, 5015-5020)and reaction with an alkyl or aryl halide, or by saponification with NaOH (DiFabio et al., 2002, J. Org. Chem., 67, 7319-7328).

Chemical name	cyclopenta[c] quinoline intermediates	Conditions of Reaction	CRX numbers	Analysis
8-Trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline-4-carboxylic acid 2,4-dichloro-benzylamide	8-Trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline-4-carboxylic acid	EDCI-DMAP-2,4-Dichloro-benzylamine CH_2Cl_2	CRX000791	ESI(+) =457
8-Trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline-4-carboxylic acid 4-chloro-benzylamide	8-Trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline-4-carboxylic acid	EDCI-DMAP-4-chloro-benzylamine CH_2Cl_2	CRX000795	ESI(+) =423
8-Trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline-4-carboxylic acid [2-(4-chloro-phenyl)-	8-Trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline-4-carboxylic acid	EDCI-DMAP-2-(4-Chloro-phenyl)-ethylamine CH_2Cl_2	CRX000827	ESI(+) =437

ethyl]-amide				
8-Trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline-4-carboxylic acid (2-ethyl-phenyl)-amide	8-Trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline-4-carboxylic acid	EDCI-DMAP-2-Ethyl-phenylamine CH_2Cl_2	CRX000874	ESI(+) =403
[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin -8-yloxy]-acetic acid	4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin-8-ol	1) Cs_2CO_3-CH_3CN Bromo-acetic acid methyl ester 2) NaOH	CRX000824	ESI(+) =390
2-[4-(2,4-Dichloro-phenyl)-3a,4,5,9 b-tetrahydro-3H-cyclopenta[c] quinolin-8-yloxy]-2-methyl-propionic acid	4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin-8-ol	1) Cs_2CO_3-CH_3CN 2-Bromo-2-methyl-propionic acid methyl ester 2) NaOH	CRX000825	ESI(+) =418
2-[3-Chloro-4-(8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenoxy]-2-methyl-propionic acid	3-Chloro-4-(8-trifluoro methoxy-3a,4 ,5,9b-tetrahydro-3H-cyclopenta[c] quinolin-4-yl)-phenol	1) Cs_2CO_3-CH_3CN 2-Bromo-2-methyl-propionic acid methyl ester 2) NaOH	CRX000900	ESI(+) =468
[3-Chloro-4-(8-trifluoro methoxy-3a, 4,5,9b-	3-Chloro-4-(8-trifluoro methoxy-3a,4 ,5,9b-	1) Cs_2CO_3-CH_3CN Bromo-acetic acid methyl	CRX000901	ESI(+) =440

tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenoxy]-acetic acid	tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenol	ester 2) NaOH		
4-(4-Benzyloxy-2-chloro-phenyl)-8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	3-Chloro-4-(8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenol	Cs_2CO_3-CH_3CN Bromomethyl-benzene	CRX000902	ESI(+) =472
4-(4-Fluoro-2-trifluoro methyl-phenyl)-8-(2,2,2-trifluoro-1-methoxy-1-trifluoro methyl-ethyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	1,1,1,3,3,3-Hexafluoro-2-[4-(4-fluoro-2-trifluoro methyl-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-propan-2-ol	Et_3N-MeI	CRX001020	APCI(+) =514

Example 19. Synthesis of N-substituted C-THQ:

The following compounds were obtained by well known reactions of alkylation or acylation (Lowden et al., 2003, J. Med. Chem., 46, 5015-5020).

Chemical name of N-substituted C-THQ	cyclopenta[c]quinoline intermediates	Conditions of Reaction	CRX numbers	Analysis
1-[4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-	4-(2,4-Dichloro-phenyl)-8-trifluoro	Trifluoro acetic Anhydride-CH_2Cl_2-DMAP-	CRX000826	ESI(+) = 498

1,2,3,3a,4,9b-hexahydro-cyclopenta[c] quinolin-5-yl]-2,2,2-trifluoro-ethanone	methoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c] quinoline	Et_3N		
4-(2,4-Dichloro-phenyl)-5-methyl-8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	4-(2,4-Dichloro-phenyl)-8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	MeI-Et_3N-DMAP	CRX000963	ESI(+) = 414
2,2,2-Trifluoro-1-(8-trifluoro methoxy-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl)-ethanone	8-Trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	Trifluoro acetic Anhydride-CH_2Cl_2-DMAP-Et_3N	CRX000947	APCI(+) = 352
5-Benzene sulfonyl-8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	8-Trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	K_2CO_3-H_2O-EtOH $PhSO_2Cl$	CRX000952	APCI(+) = 396
5-(2,4-Dichloro-benzyl)-8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	8-Trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinoline	K_2CO_3-CH_3CN-(2,4-dichloro)-$PhCH_2Cl$-reflux	CRX000978	APCI(+) = 414
2-[5-(2,4-Dichloro-benzyl)-3a,4,5,9 b-tetrahydro-3H-cyclopenta[c]	1,1,1,3,3,3-Hexafluoro-2-(3a,4,5,9b-tetrahydro-3H-cyclopenta[c] quinolin-8-	K_2CO_3-CH_3CN-(2,4-dichloro)-$PhCH_2Cl$-reflux	CRX001021	APCI(+) = 476

quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol	yl)-propan-2-ol			
2,2,2-Trifluoro-1-[8-(2,2,2-trifluoro-1-hydroxy-1-trifluoro methyl-ethyl)-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl]-ethanone	1,1,1,3,3,3-Hexafluoro-2-(3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)-propan-2-ol	Trifluoro acetic Anhydride-CH_2Cl_2-DMAP-Et_3N	CRX001064	APCI(+) = 434
5-Methyl-8-(2,2,2-trifluoro-1-methoxy-1-trifluoromethyl-ethyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	1,1,1,3,3,3-Hexafluoro-2-(3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)-propan-2-ol	MeI-Et_3N-DMAP	CRX000972	^{1}H NMR ($CDCl_3$) δ= 2.0 (d, 1H), 2.6 (m, 1H), 2.7 (m, 2H), 2.8 (s, 3H), 2.9 (d, 1H), 3.4 (s, 3H), 3.7 (bs, 1H), 5.7 (m, 2H), 6.6 (d, 1H), 7.2 (m, 2H)
1-[4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl]-propan-1-one	4-(2,4-Dichloro-phenyl)-8-trifluoro methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	$MeCH_2COCl$-BuLi	CRX000793	APCI(+) = 456

Example 20 : Preparation of enantiomerically pure C-THQ compounds

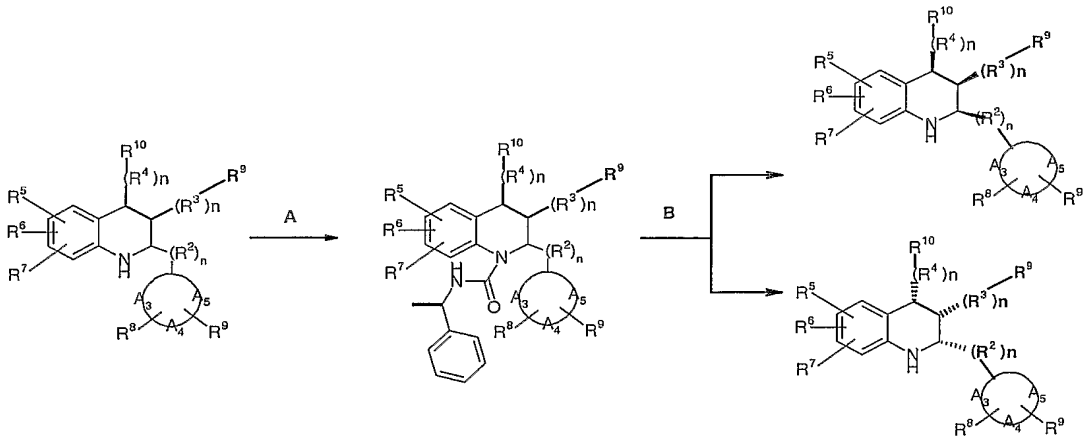
Enantiomerically pure syn C-THQ compounds have been obtained either by chiral HPLC separation or by resolution using a chiral auxiliary. Their references are provided in the Table below :

C-THQ	Name	Enantiopur C-THQ	Optical rotation ($CHCl_3$)
CRX156651	4-(2,4-dichloro-phenyl)-8-trifluoro-methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX000908	-7.4 (c = 2.2)
		CRX000909	+6.9 (c = 2.0)
CRX000425	4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline	CRX001075	+59.2 (c = 0.37)
		CRX001076	-69.5 (c = 0.2)
CRX000369	4-(2,4-Dichloro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline	CRX001045	-22.4 (c = 0.78)
		CRX001046	+20.9 (c = 0.43)
CRX000860	1,1,1,3,3,3-Hexafluoro-2-[4-(4-fluoro-2-trifluoromethyl-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-propan-2-ol	CRX001072	-27.5 (c = 0.12)
		CRX001074	+29.0 (c = 0.1)
CRX000935	6-(2,4-Dichloro-phenyl)-2-trifluoromethoxy-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinoline	CRX001102	+268 (c = 0.07)
		CRX001059	-300 (c = 0.005)

Example 20.1 Preparative method for chiral HPLC separation:

Compound	Column	Mobile phase	Flow rate	Detection UV	Temperature
CRX156651	250*50 mm CHIRALPAK ® AD 20 µm	MeOH	120ml/min	320 nm	room
CRX000369	250*50 mm CHIRALPAK ® AD 20 µm	MeOH	120ml/min	300 nm	room
CRX000425	250*50 mm CHIRALPAK ® AD 20 µm	MeOH	120ml/min	310 nm	room
CRX000860	250*50 mm CHIRALPAK ® AD 20 µm	Heptane /IPA 95/5	120ml/min	300 nm	room

Example 20.2 Resolution of racemic mixture :



Step A : formation of urea diastereomers ;

Step B : separation of diastereomers followed by deprotection of the urea function

Example 20.2a : General procedure for synthesis of diastereomer

To a solution of racemic THQ compound (1 eq.) in THF at -78°C, was added nBuLi (1.5 eq.), followed after 10 min by (*R*) or (*S*) isocyanate (1.4 eq.). The reaction was then stirred 12hrs at 25°C. The solution was washed with water and extracted with CH_2Cl_2. After evaporation of the solvents, the diastereomers were purified and separated by flash chromatography (EtOAc/Hexane 1:9).

Example 20.2b : General procedure for deprotection with HBr

A solution of the pure diastereomer (0.5 mmol) in 5 mL of HBr 33% in CH_3COOH was stirred at 60°C for 24hrs. After evaporation of the solvents, the residue was purified by flash chromatography (EtOAc/Hexane 1:9) to give the enantiomerically pure compound.

Example 20.2c : General procedure for deprotection with TFA

A solution of pure diastereomer (2.8 mmol) in TFA/CH_2Cl_2 (20mL/20 mL) was stirred at 60°C for 24hrs. After evaporation of the solvents, the the residue was purified by flash chromatography (EtOAc/Hexane 1:9) to give the enantiomerically pure compound.

Example 21 : Compounds of the invention bind to the human LXR alpha and beta

Recombinant GST-LBD-LXR alpha and beta protein

The LBD of human LXRalpha and LXRbeta (amino acids 164 - 447 and 155 - 461, respectively) were expressed as amino-terminal Glutathione S-Transferase (GST) fusion protein in the BL21(DE3) *E. coli* strain (Invitrogene). One-liter cell cultures consisting of standard Terrific broth (TB) medium

with 0.06 mg/ml ampicillin were inoculated and grown at 25°C for 4 h. When cells reached a density of $0.8>DO_{600}>1$, the cells were induced with 0.1 mM isopropyl ß-D-thiogalactopyranoside for 3h at 4°C. The cells were harvested by centrifugation (8 min, 7,500 x *g*, 4°C). The cell pellet was re-suspended in 100 ml TBS-T buffer (50 mM Tris-Cl pH 8.0, 100 mM NaCl, 0.05% Triton X100, 0.5mM DTT), homogenized with Emulsiflex C-5 at 15000 psi (2x) at 4°C and centrifuged (30 min, 45,000 x *g*, 4°C). Gluthatione Sepharose beads (800μl, Amersham Biosciences) were incubated with supernatant for 1h at 4°C. Following washing with TBS-T and T buffers (Tris 50mM, pH 8), the GST-hLXRalpha-LBD or GST- hLXRbeta-LBD protein was eluted using 2.4 ml T buffer containing 40 mM glutathione, pH 7.5. To exchange the buffer was achived by size exclusion chromatography, using a pre-packed PD10 column (Amersham Biosciences) pre-equilibrated with 20 mM Tris-Cl, pH 8.0, 200 mM NaCl, 5 mM dithiothreitol, 2.5 mM EDTA, pH 8.0. The proteins were concentrated using Centri-prep 30K (Amicon).

Results

Scintillant-filled beads precoated with poly-(L)-lysine to permit protein binding (Amersham) were diluted in scintillation proximity assay (SPA) buffer [10 mM Na_2HPO_4,10 mM NaH_2PO_4, 2mM EDTA, 50 mM NaCl, 1 mM DTT, 2 mM 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate, 10% glycerol, pH=8] to a final concentration of 50 mg/ml. Binding assays were performed in 96-well plates (Packard) in a total volume of 100 microl containing beads (0.2 mg per well) and GST-hLXRalpha-LBD and GST- hLXRbeta-LBD (150 and 100 ng per well, respectively). [^{3}H]-T0901317 was diluted in SPA buffer and added to wells for a final concentration of 45 nM. In competition binding assays, unlabeled compounds of the invention were serially diluted in SPA buffer, then added at final concentrations ranging from 0.1 to 10 000 nM. Plates

were incubate at 4°C for 1 h, and then radioactivity was measured with a Packard Topcount at 1 min per well. All concentrations were assayed in duplicate. Competition curves were generated by nonlinear regression analysis using Graphpad Prism.

Table 1 shows Ki values for compounds of the invention for LXR alpha and LXR beta.

Compound	hLXRa Ki (nM)	hLXRb Ki (nM)
CRX000292	250-1000	1000-3000
CRX000480	250-1000	1000-3000
CRX000483	250-1000	250-1000
CRX000558	1000-3000	1000-3000
CRX000569	250-1000	1000-3000
CRX000593	250-1000	1000-3000
CRX000599	250-1000	1000-3000
CRX000612	250-1000	1000-3000
CRX000646	1000-3000	1000-3000
CRX000744	25-250	1000-3000
CRX000860	25-250	25-250
CRX000903	250-1000	1000-3000
CRX000908	25-250	250-1000
CRX000909	1000-3000	> 3000
CRX000927	25-250	25-250
CRX000966	25-250	25-250
CRX000973	250-1000	250-1000
CRX000997	250-1000	1000-3000
CRX001075	25-250	250-1000
CRX001076	1000-3000	1000-3000
CRX001084	250-1000	1000-3000
CRX001085	250-1000	250-1000
CRX156651	250-1000	1000-3000

Table 1

Example 22. Compounds of the invention activate human LXR alpha and beta

The CV1 cell lines were obtained from ATCC (Rockville, MD). Cells were maintained in Dulbecco's modified Eagle's minimal essential medium (DMEM) supplemented with 10 % foetal calf serum (FCS), L-glutamine (2 mM), and antibiotics (penicillin/streptomycin). In order to test the ability of compounds of the invention to activate human LXR alpha and beta, CV1 cells (2.5 x 10^4 cells per well of a 96 wells

plate) were grown at 37°C under a 5% CO_2 atmosphere in DMEM medium supplemented with 10% lipid deficient serum.

Cotransfection was performed by adding in each well 0.2 ng of hLXR alpha or beta plasmid, 8 ng of the luciferase reporter plasmid, 8 ng of pCMV-betaGAL plasmid and 72 ng of a carrier plasmid (pBluescript, Statagene). In case of human LXR beta transfection, 8 ng of PGC1alpha expression plasmid were included. Said co-transfection was realised using the FuGENE 6 transfection reagent (Roche) according to the manufacturer's instructions.

After about 16 hours of growth, the medium was changed by fresh supplemented DMEM. Cells were treated with increasing doses (from 1.10^{-10} to 1.10^{-5} M) of T0901317 or compounds of the invention and incubated for 24 hours as mentioned above.

Cells were lysed with 100 µl of lysis buffer (40 mM TRIS pH 7.8, 2.14 mM $MgCl_2$, 5.4 mM $MgSO_4$, 0.2 mM EDTA, and 66.6 mM DTT). 50 µl of the lysate were subjected to luciferase assay, whereas 30 µl of lysate were used for beta-galactosidase assay. The luciferase data were normalised to beta-galactosidase activity and data the EC50 were calculated using Graphpad Prism.

Table 2 shows EC50 values for compounds of the invention for LXR alpha and LXR beta.

Compound	hLXRa EC50 (nM)	hLXRb EC50 (nM)
CRX000292	1000-3000	250-1000
CRX000480	250-1000	250-1000
CRX000860	1000-3000	250-1000
CRX000908	250-1000	250-1000
CRX000927	250-1000	250-1000
CRX000966	1000-3000	1000-3000
CRX000973	250-1000	250-1000
CRX000997	250-1000	1000-3000
CRX156651	250-1000	250-1000

Table 2

Example 23. Compounds of the invention activate gene implicated in cholesterol efflux

The THP-1 cells were obtained from ATCC (Rockville, MD). Cells were maintained in RPMI 1640 medium (GIBCO) supplemented with 10 % foetal bovine serum, sodium pyruvate (1 mM), HEPES (10 mM), beta-mercapto-ethanol (0.05 mM), L-glutamine (2 mM) and antibiotics (penicillin/streptomycin). In order to test the ability of compounds of the invention to activate gene implicated in cholesterol efflux, the ABCA1 gene, the THP-1 cells (2.5 x 10^4 cells per well of a 96 wells plate) were differentiated at 37°C under a 5% CO_2 atmosphere in RPMI medium supplemented with 0.2 μM phorbol 12-myristate-13-acetate (SIGMA). The medium was change every third day.

After 5 days of differentiation, the medium was changed by fresh RPMI medium supplemented with 10% lipid deficient medium. Cells were treated with increasing doses of T0901317 or compounds of the invention and incubated for 24 hours as mentioned above.

Real time quantitative PCR was used to determine the relative levels of ABCA1 mRNA. Total RNAs were isolated using the SV Total RNA Isolation System (Promega) according to the instructions from the manufacturer. RNAs were converted to a single stranded cDNA with the Reverse Transcription system (AMV, Promega) and random primers following the recommendations of the manufacturer, in a 96 wells plate in a thermocycler at 42 °C for 1 hour. RNA levels were measured by quantitative PCR using the LightCycler-FastStart DNA SYBRGreen I kit (Roche Diagnostics) on the LightCycler system (Roche Diagnostics). Primers (5′-TGTCCAGTCCAGTAATGGTTCTGTGT-3′ and 5′-GCGAGATATGGTCCGGATTG-3′) were as described in Oliver *et al.* (Oliver, et al., 2001, Proc Natl Acad Sci U S A., 98, 5306-5311). 40 PCR cycles were performed essentially as described by the manufacturer with 2 μl of cDNA in the

presence of 0.4 μM of each primer, 3 mM $MgCl_2$ with an annealing at 60 °C and extension at 72 °C for 19 seconds. The specificity of the fluorescence signal was verified by a melting curve analysis at the end of the run. The quantification was performed based on the CP determination obtained via the Second Derivative Maximum Method from the LightCycler. The relative expression ratio of the target gene in a sample X compared to a calibrator or control sample is described by the equation: $Ratio=E^{-CPx-CPcont}$ (Pfaffl, et al., 2002, Nucleic Acids Res. 30, 36); with E representing the PCR efficiency for each pair of primers. Samples were analysed in duplicate.

Table 3 shows ABCA1 gene expression data expressed as percentage maximal induction obtained with the reference compound T0901317 treatment for the compounds of the invention.

Compound	ABCA1 % of Vmax
CRX000369	80-100
CRX000563	80-100
CRX000860	50-80
CRX000908	80-100
CRX000909	< 30
CRX001075	80-100
CRX001076	80-100
CRX156651	50-80

Table 3

Example 24. Compounds of the invention show reduced activation of genes implicated in lipogenesis compared to reference compounds known in the art.

The HepG2 cells were obtained from ATCC (Rockville, MD). Cells were maintained in MEM medium (GIBCO) supplemented with 10 % foetal bovine serum, non essential amino acids (0.1 mM), sodium pyruvate (1 mM), L-glutamine (2 mM) and antibiotics (penicillin/streptomycin). In order to test the ability of compounds of the invention to activate genes implicated in

lipogenesis, fatty acid synthase (FAS) and sterol response element binding protein 1c (SREBP1c), the HepG2 cells (2.5 x 10^4 cells per well of a 96 wells plate) were grown at 37°C under a 5% CO_2 atmosphere in MEM medium supplemented with 10% lipid deficient serum.

After 24 hours, the medium was changed by fresh medium supplemented with 10% lipid deficient medium. Cells were treated with increasing doses of T0901317 or compounds of the invention and incubated for 24 hours as mentioned above.

Real time quantitative PCR was used to determine the relative levels of FAS mRNA. Total RNAs were isolated by using the SV Total RNA Isolation System (Promega) according to the instructions from the manufacturer. RNAs were converted to a single stranded cDNA with the Reverse Transcription system (AMV, Promega) and random primers following the recommendations of the manufacturer, in a 96 wells plate in a thermocycler at 42°C for 1 hour. RNA levels were measured by quantitative PCR using the LightCycler-FastStart DNA SYBRGreen I kit (Roche Diagnostics) on the LightCycler system (Roche Diagnostics). Oligonucleotide primers 5′-GGTGTTTGTCTGTGTTTGTTTTTCA-3′ and 5′-AGATCACATGCGGTTTAATTGTGG-3′ for FAS and 5′-GCGGAGCCATGGATTGCAC-3′ and 5′-CTCTTCCTTGATACCAGGCCC-3′ for SREBP1c, respectively were designed using the Probe Design program (Roche Diagnostics) and synthetised by Genset. 40 PCR cycles were performed essentially as described by the manufacturer with 2 µl of cDNA (1/10 dilution for FAS) in the presence of 0.4 µM of each primer, 3 mM $MgCl_2$ and annealing at 60 °C and extension at 72 °C for 19 seconds. The specificity of the fluorescence signal was verified by a melting curve analysis at the end of the run. The quantification was performed based on the CP determination obtained via the Second Derivative Maximum Method from the LightCycler. The relative expression ratio of the target gene

in a sample X compared to a calibrator or control sample is described by the equation: $Ratio=E^{-CPx-CPcont}$ (Pfaffl, et al., 2002, Nucleic Acids Res. 30, 36); with E representing the PCR efficiency for each pair of primers. Samples were analysed in duplicate.

Table 4 shows FAS and SERBP1c gene expression data expressed as percentage maximal induction obtained with the reference compound T0901317 treatment for the compounds of the invention.

Compound	FAS % of Vmax	SREBP1c % of Vmax
CRX000369	< 30	50-80
CRX000563	30-50	50-80
CRX000860	< 30	< 30
CRX000908	30-50	50-80
CRX000909	< 30	< 30
CRX001075	30-50	30-50
CRX001076	< 30	< 30
CRX156651	30-50	30-50

Table 4

Example 25. Compounds of the invention show reduced activation of genes regulating plasma triglyceride levels compared to reference compound of the art.

The HepG2 cells were obtained from ATCC (Rockville, MD). Cells were maintained in MEM medium (GIBCO) supplemented with 10 % foetal bovine serum, non essential amino acids (0.1 mM), sodium pyruvate (1 mM), L-glutamine (2 mM) and antibiotics (penicillin/streptomycin). In order to test the ability of compounds of the invention to activate a gene regulating plasma triglyceride levels, angiopoietin-like protein 3 (Angptl3), the HepG2 cells (2.5×10^4 cells per well of a 96 wells plate) were grown at 37°C under a 5% CO_2 atmosphere in MEM medium supplemented with 10% lipid deficient serum.

After 24 hours, the medium was changed by fresh medium supplemented with 10% lipid deficient medium. Cells were

treated with increasing doses of T0901317 or compounds of the invention and incubated for 24 hours as mentioned above.

Real time quantitative PCR was used to determine the relative levels of Angptl3 mRNA. Total RNAs were isolated by using the SV Total RNA Isolation System (Promega) according to the instructions from the manufacturer. RNAs were converted to a single stranded cDNA with the Reverse Transcription system (AMV, Promega) and random primers following the recommendations of the manufacturer, in a 96 wells plate in a thermocycler at 42°C for 1 hour. RNA levels were measured by quantitative PCR using the LightCycler-FastStart DNA SYBRGreen I kit (Roche Diagnostics) on the LightCycler system (Roche Diagnostics). Oligonucleotides primers 5′-TCAATGAAACGTGGGAGA-3′ and 5′-TTGCCAGTAATCGCAAC-3′ were designed using the Probe Design program (Roche Diagnostics) and synthetised by Genset. 40 PCR cycles were performed essentially as described by the manufacturer with 2 μl of cDNA in the presence of 0.4 μM of each primer, 3 mM $MgCl_2$ and annealing at 58 °C and extension at 72 °C for 19 seconds. The specificity of the fluorescence signal was verified by a melting curve analysis at the end of the run. The quantification was performed based on the CP determination obtained via the Second Derivative Maximum Method from the LightCycler. The relative expression ratio of the target gene in a sample X compared to a calibrator or control sample is described by the equation: $Ratio=E^{-CPx-CPcont}$ (Pfaffl, et al., 2002, Nucleic Acids Res. 30, 36); with E representing the PCR efficiency for each pair of primers. Samples were analysed in duplicate.

Table 5 shows Angptl3 gene expression data expressed as percentage maximal induction obtained with the reference compound T0901317 treatment for the compounds of the invention.

Compound	Angptl3 % of Vmax
CRX000369	< 30
CRX000563	30-50
CRX000860	< 30
CRX000908	30-50
CRX000909	< 30
CRX001075	50-80
CRX001076	< 30
CRX156651	< 30

Table 5

Example 26. Compounds of the invention promote cholesterol efflux *in vitro*

The THP-1 cells were obtained from ATCC (Rockville, MD). Cells were maintained in RPMI 1640 medium (GIBCO) supplemented with 10 % foetal bovine serum, sodium pyruvate (1 mM), HEPES (10 mM), beta-mercapto-ethanol (0.05 mM), L-glutamine (2 mM) and antibiotics (penicillin/streptomycin). In order to test the ability of compounds of the invention to stimulate cholesterol efflux, the THP-1 cells (1.5×10^5 cells per well of a 48 wells plate) were differentiated at 37°C under a 5% CO_2 atmosphere in RPMI medium supplemented with 0.2 μM phorbol 12-myristate-13-acetate (SIGMA). The medium was change every third day.

After 5 days of differentiation, the cells were loaded for 24 h with 50μg/ml acetylated LDL (Intracel) and 1 μCi/ml [^{3}H] cholesterol (Amersham) in the medium supplemented with 10% lipid deficient medium. Cells were washed twice with phosphate saline buffer and equilibrated in RPMI 1640 medium (GIBCO) supplemented with 0.2 % bovine serum albumin, sodium pyruvate (1 mM), HEPES (10 mM), beta-mercapto-ethanol (0.05 mM), L-glutamine (2 mM) and antibiotics (penicillin/streptomycin) for 4 hours. Cells were washed with phosphate saline buffer and then treated with the compounds of the invention at final concentration 3μM for 16 h with or

without 15 μg/ml ApoAI (Intracel). Medium was collected and centrifuged at 14,000 rpm for 2 min to remove debris. Cholesterol was extracted with 250 μl of isopropanol. Scintillation counts were taken of medium and cells. The percentage of efflux was determined for each well using the formula: counts media/(counts cells +counts media)*100. The experiment was performed in quadruplicate.

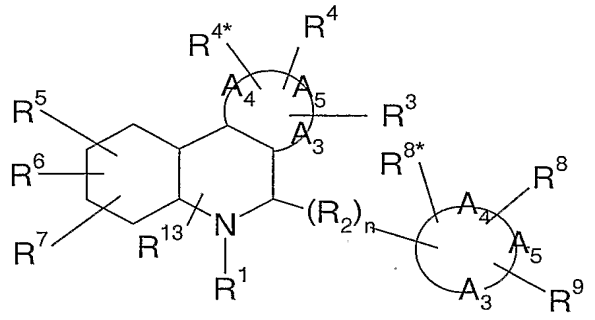
Table 6 shows cholesterol efflux data expressed as percentage of cholesterol efflux obtained with the reference compound T0901317 treatment for the compounds of the invention.

Compound	Chol. efflux % of Vmax
CRX000908	80-100

Table 6

CLAIM

1. A compound of the following general formula (I):



or analogues, derivatives, solvates or salts thereof,

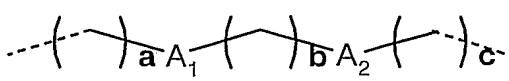
wherein :

R^1 is a moiety selected in the group consisting of -H, -Cl, -F, $-C_{n'}H_{2n'+1}$, $-CO-C_{n'}H_{2n'+1}$, $-O-C_{n'}H_{2n'+1}$, $-CO-O-C_{n'}H_{2n'+1}$, a cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety or a cycloheptyl), a $-(CH_2)_n-$ cycloalkyl moiety (e.g. a $-(CH_2)_n-$cyclohexyl or a $-(CH_2)_n$-phenyl moiety or a $-(CH_2)_n-$cycloheptyl), $-SO_2CF_3$, $-CF_3$, $-CO-CF_3$, $-O-CF_3$, $-(CH_2)_n-CF_3$, $-SO_2-(CH_2)_n-C_{n'}H_{2n'+1}$, ,$-SO_2-(CH_2)_n-$ cycloalkyl moiety (e.g. a $-SO_2-(CH_2)_n$-cyclohexyl or a $-SO_2-(CH_2)_n$-phenyl moiety) or $-SO_2-(CH_2)_n$-cycloheptyl), $-CO-(CH_2)_n-C_{n'}H_{2n'+1}$, $-CO-(CH_2)_n$-cycloalkyl moiety (e.g. a $-CO-(CH_2)_n$-cyclohexyl or a $-CO-(CH_2)_n$-phenyl moiety) or a $-CO-(CH_2)_n$-cycloheptyl);

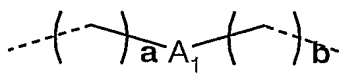
R^2 , R^{11} are, independently from one another, a moiety selected in the group consisting of :

(i) CH_2

(ii)



(iii)



with :

a, **b** and **c** are, independently from one another, an integer ranging from 0 to 4 ;

$\mathbf{A_1}$ and $\mathbf{A_2}$ are, independently from one another, a moiety selected in the group consisting of -CO-, -O-, $-SO_2-$, -CH-, $-CH_2-$, -NH-, $-N(C_{n'}H_{2n'+1})$, -N(cycloalkyl)- [e.g. -N(cyclohexyl)- or -N(phenyl)-] and -CHOH- ;

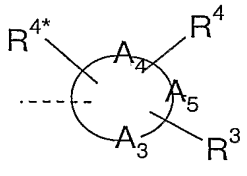
$\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^{4*}}$, $\mathbf{R^8}$, $\mathbf{R^{8*}}$, $\mathbf{R^9}$ are, independently from one another, a moiety selected in the group consisting of H, -Cl, $-CF_3$, -F, -Br, -CN, $-C_{n'}H_{2n'+1}$, a cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety or a cycloheptyl), $-(CH_2)_nCO_2H$, $-CH(CH_2)_2$, $-(CH_2)_n-CO-C_{n'}H_{2n'+1}$, $-(CH_2)_n-CO-$cycloalkyl (e.g. $-(CH_2)_n$ -CO-cyclohexyl or $-(CH_2)_n$ -CO-phenyl), $-(CH_2)_n-$cycloalkyl (e.g. $-(CH_2)_n-$cyclohexyl or $-(CH_2)_n-$phenyl), -OH, $-OCF_3$, $-OC_{n'}H_{2n'+1}$, $-O-(CH_2)_n-$ cycloalkyl (e.g. $-O-(CH_2)_n-$cyclohexyl or $-O-(CH_2)_n-$phenyl), $-O-(CH_2)_nCO_2H$, -COH, $-CO-C_{n'}H_{2n'+1}$, $-CO-(CH_2)_n-$cycloalkyl (e.g. $-CO-(CH_2)_n-$cyclohexyl or $-CO-(CH_2)_n-$phenyl), $-CO-(CH_2)_nCO_2H$, $-O-CO-(CH_2)_n-$cycloalkyl (e.g. $-O-CO-(CH_2)_n-$cyclohexyl or $-O-CO-(CH_2)_n-$phenyl), -O-benzoyl, $-SO_2H$, $-SO_2-C_{n'}H_{2n'+1}$, $-SO_2-(CH_2)_n-$ cycloalkyl (e.g. $-SO_2-(CH_2)_n-$cyclohexyl or $-SO_2-(CH_2)_n-$phenyl), $-SO_2-CO-(CH_2)_n-$ cycloalkyl (e.g. $-SO_2-CO-(CH_2)_n-$cyclohexyl or $-SO_2-CO-(CH_2)_n-$phenyl), $-SO_2-CO-$(cycloalkyl (e.g. $-SO_2-CO-$cyclohexyl or $-SO_2-CO-$phenyl), $-O-SO_2H$, $-O-SO_2-C_{n'}H_{2n'+1}$, $-O-SO_2-(CH_2)_n-$ cycloalkyl (e.g. $-O-SO_2-(CH_2)_n-$cyclohexyl or $-O-SO_2-(CH_2)_n-$phenyl), $-O-SO_2-CO-(CH_2)_n-$ cycloalkyl (e.g. $-O-SO_2-CO-(CH_2)_n-$cyclohexyl or $-O-SO_2-CO-(CH_2)_n-$phenyl), $-O-SO_2-CO-$

(cycloalkyl (e.g. -O-SO_2-CO-cyclohexyl or -O-SO_2-CO-phenyl), -NO_2, -NH_2, -NH($C_{n'}H_{2n'+1}$), -N($C_{n'}H_{2n'+1}$)($C_{n'}H_{2n'+1}$), -NH-$(CH_2)_n$-cycloalkyl (e.g. -NH-$(CH_2)_n$-cyclohexyl or -NH-$(CH_2)_n$-phenyl), -NH-CO-$(C_{n'}H_{2n'+1})$, -NH-CO-$(CH_2)_n$-cycloalkyl (e.g. -NH-CO-$(CH_2)_n$-cyclohexyl or -NH-CO-$(CH_2)_n$-phenyl), -NH-CO-cycloalkyl (e.g. -NH-CO-cyclohexyl or -NH-CO-phenyl), -SH, -$SC_{n'}H_{2n'+1}$, -S-$(CH_2)_n$-cycloalkyl (e.g. -S-$(CH_2)_n$-cyclohexyl or -S-$(CH_2)_n$-phenyl), -S-CO-$(CH_2)_n$- cycloalkyl (e.g. -S-CO-$(CH_2)_n$-cyclohexyl or -S-CO-$(CH_2)_n$-phenyl), -S-CO-(cycloalkyl (e.g. -S-CO-cyclohexyl or -S-CO-phenyl), -$(CH_2)_n$-N(R^{10})(R^{10*}), -$(CH_2)_n$-CO-N(R^{10})(R^{10*}), -O-SO_2-N(R^{10})(R^{10*}), -CO-SO_2-N(R^{10})(R^{10*}), -SO_2-N(R^{10})(R^{10*}), -NR^{10}-SO_2CF_3, -NR^{10}-SO_2($C_{n'}H_{2n'+1}$), with $\mathbf{R^{10}}$ and $\mathbf{R^{10*}}$ are, independently from one another, a moiety selected in the group consisting of H and a C_{1-4} alkyl moiety ;

$\mathbf{R^{13}}$ is a moiety selected in the group consisting of H, -$C_{n'}H_{2n'+1}$, -$(CH_2)_nCO_2H$, -$CH(CH_2)_2$, -$(CH_2)_n$-CO-$C_{n'}H_{2n'+1}$, -OH, -OCF_3, -$OC_{n'}H_{2n'+1}$, -O-$(CH_2)_nCO_2H$, -COH, -CO-$C_{n'}H_{2n'+1}$, -CO-$(CH_2)_nCO_2H$, -O-benzoyl, -SO_2H, -SO_2-$C_{n'}H_{2n'+1}$, -O-SO_2H, -O-SO_2-$C_{n'}H_{2n'+1}$, -NO_2, -NH_2, -NH($C_{n'}H_{2n'+1}$), -N($C_{n'}H_{2n'+1}$)($C_{n'}H_{2n'+1}$), -NH-CO-$(C_{n'}H_{2n'+1})$, -SH, -$SC_{n'}H_{2n'+1}$, -$(CH_2)_n$-N(R^{10})(R^{10*}), -$(CH_2)_n$-CO-N(R^{10})(R^{10*}), -O-SO_2-N(R^{10})(R^{10*}), -CO-SO_2-N(R^{10})(R^{10*}), -SO_2-N(R^{10})(R^{10*}), -NR^{10}-SO_2CF_3, -NR^{10}-SO_2($C_{n'}H_{2n'+1}$);

$\mathbf{R^5}$, $\mathbf{R^6}$ and $\mathbf{R^7}$ are, independently from one another, a moiety of the following general formula : -$(R^{11})_n$-R^{12} ;

$\mathbf{R^{12}}$ is a moiety selected in the group consisting of -H, -$C_{n'}H_{2n'+1}$, -N($C_{n'}H_{2n'+1}$)($C_{n'}H_{2n'+1}$), -NO_2, -Cl, -Br, -CN, -F, -CF_3, -OH, -$(CH_2)_n$-COOH, -C(OH)$(CH_3)_2$, -C(OH)$(CF_3)_2$, -SO_2CF_3, -SO_2($C_{n'}H_{2n'+1}$) and :



;

A_3, A_4 and A_5 are, independently from one another, an atom selected in the group consisting of C, N, O and S ;

with in all the above :

n is, independently from one another, an integer ranging from 0 to 6,

n' is, independently from one another, an integer ranging from 1 to 8, preferably from 1 to 4, preferably from 1 to 3 and more preferably from 1 to 2.

2. The compound of claim 1 wherein the moiety :

is intended to designate :

(i) a mono carbocyclic ring (i.e. a cyclic carboalkyl, with A_3, A_4 and A_5 are C)

(ii) a mono heterocyclic ring (i.e. a cyclic heteroalkyl, with at least one A_3, A_4 and/or A_5 is selected in the group consisting of N, S and O)

(iii) a bi- carbocyclic ring (i.e. a bicyclic carboalkyl with A_3, A_4 and A_5 are C)

(iv) a bi- heterocyclic ring (i.e. a bicyclic heteroalkyl with at least one cyclic ring is containing at least one A_3, A_4 and/or A_5 selected in the group consisting of N, S and O).

3. A compound of claims 1 to 2 selected in the group consisting in :

1-[4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanone,

4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX156651 or CRX000908 or CRX00909) ,

1-[4-(2-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanone,

4-(4-Nitro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-Naphthalen-1-yl-3a,4,5,9b-tetrahydro-3Hcyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanone,

4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

4-(2-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

4-(2,3-Dichloro-phenyl)-8-nitro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

8-Chloro-4-(2-chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(2,4-Dichloro-phenyl)-8-methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid methyl ester,

4-(4-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,

4-(2-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid ethyl ester,

4-(4-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid ethyl ester,

4-(3-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester,
4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid,
4-(4-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid,
4-(3-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid,
4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid,
4-(2-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid,
4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid,
4-(4-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-6-carboxylic acid,
4-(4-Nitro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid diethylamide,
4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid diethylamide,
4-(4-Chloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid diethylamide,
[4-(4-Bromo-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-6-yl]-morpholin-4-yl-methanone,
4-Furan-2-yl-8-methoxy-2,3,3a,4,5,9b-hexahydro-furo[3,2c]quinoline,
4-Phenyl-2,3,3a,4,5,9b-hexahydro-furo[3,2c]quinoline,
4-(2-Methoxy-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,
4-(2-Chloro-4-fluoro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline ,
4-(2-Nitro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-Biphenyl-4-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(2-Chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(4-Chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(3-Fluoro-2-methyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(2-Ethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(2,3-Dimethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

8-Trifluoromethoxy-4-(2-trifluoromethyl-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

4-(2-Fluoro-3-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

[3-Chloro-4-(8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenyl]-dimethyl-amine,

4-(2-Chloro-3-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline,

2-(8-Trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-phenylamine,

4-(2-Chloro-4-fluoro-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline,

4-Biphenyl-4-yl-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline,

4-(2-Methoxy-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline,

4-(2-Chloro-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline,

4-(4-Chloro-phenyl)-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline,

4-(2,3-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000292)

4-Phenyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000293)

1-[4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl]-2,2,2-trifluoro-ethanone (CRX 000295)

4-Furan-2-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000319)

2-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol (CRX 000321)

2-[4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol (CRX 000322)

4-(2,3-Dichloro-phenyl)-8-methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000361)

4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-ol (CRX 000368)

4-(2,4-Dichloro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000369 or CRX001045 or CRX001046)

4-(2,3-Dichloro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000370)

4-(2,4-Dichloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000374)

1-(4-Furan-2-yl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)-ethanone (CRX 000387)

4-Thiophen-2-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000406)

4-(2,6-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000409)

4-Naphthalen-1-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000412)

4-Benzyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline(CRX 000413)

4-Cyclohexyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000415)

5-Benzyl-4-(2,4-dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000416)

4-Thiophen-3-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000429)

4-Thiazol-2-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000430)

4-Pyridin-4-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000507)

4-(5-Phenyl-thiophen-2-yl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000508)

4-(2,3-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester (CRX 000525)

4-Phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid ethyl ester (CRX 123505)

4-(2-Methoxy-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline(CRX 000558)

4-(2-Chloro-4-fluoro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000564)

4-(2-Nitro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000567)

4-Biphenyl-4-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000568)

4-(2-Chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000569)

4-(4-Chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000570)

4-(3-Fluoro-2-methyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000593)

4-(2-Ethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000595)

4-(2,3-Dimethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000596)

8-Trifluoromethoxy-4-(2-trifluoromethyl-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000612)

4-(2-Fluoro-3-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000613)

[3-Chloro-4-(8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenyl]-dimethyl-amine (CRX000614)

4-(2-Chloro-3-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX000646)

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000320)

4-(3-Nitro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000323)

4-Methyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000408)

4-tert-Butyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000410)

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid ethyl ester(CRX000414)

4-(4-Fluoro-2-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000740)

8-Trifluoromethoxy-4-(4-trifluoromethoxy-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000741)

4-(4-Ethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000742)

3-Chloro-4-(8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenol (CRX 000743)

4-(2,4-Bis-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000744)

4-(2-Fluoro-4-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000745)

4-(3,5-Dichloro-pyridin-4-yl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000763)

4-(3,4-Dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000764)

4-Cyclopropyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000863)

4-Piperidin-4-yl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000899)

4-(2-Chloro-4-methoxy-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000903)

4-(8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-piperidine-1-carboxylic acid tert-butyl ester (CRX 000905)

4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000737)

4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-ol (CRX 000738)

4-(2,4-Dichloro-phenyl)-8-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000739)

4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carbonitrile (CRX 000746)

[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-acetic acid (CRX 000747)

[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-dimethyl-amine (CRX 000794)

[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-methanol (CRX 000896)

4-Cyclohexyl-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000977)

4-(4-Fluoro-2-trifluoromethyl-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000997)

4-(2-Nitro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001000)

6-Chloro-4-(2,4-dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001066)

N-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-methanesulfonamide (CRX 001018)

1,1,1,3,3,3-Hexafluoro-2-(3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)-propan-2-ol (CRX 000971)

1,1,1,3,3,3-Hexafluoro-2-[4-(4-fluoro-2-trifluoromethyl-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-propan-2-ol (CRX 000860)

2-(4-Cyclohexyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)-1,1,1,3,3,3-hexafluoro-propan-2-ol(CRX 000861)

4-(2,4-Dichloro-phenyl)-7-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000792)

4-(2,4-Bis-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 000969)

6-Chloro-4-(2,4-dichloro-phenyl)-8-trifluoromethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001083)

7-Chloro-4-(2,4-dichloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001084)

6-Chloro-4-(4-fluoro-2-trifluoromethyl-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001087)

6-Chloro-4-phenyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001088)

6-Chloro-4-cyclohexyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001113)

4-(2,4-Dichloro-phenyl)-8-isopropyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (CRX 001114)

1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-2,2,2-trifluoro-ethanone (CRX001085)

4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylic acid amide (CRX 000760)

4-(2,4-dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-ylamine (CRX 000765)

2-[4-(2,4-Dichloro-phenyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol (CRX000927)

2,2,2-Trifluoro-1-(8-trifluoromethoxy-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]quinolin-5-yl)-ethanone (CRX000953)

8-Trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline (CRX000961)

1,1,1,3,3,3-Hexafluoro-2-[4-(4-fluoro-2-trifluoromethyl-phenyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-8-yl]-propan-2-ol (CRX000966)

4-Cyclohexyl-8-trifluoromethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline (CRX000990)

4-(4-Fluoro-2-trifluoromethyl-phenyl)-8-trifluoromethyl-2,3,3a,4,5,9b-hexahydro-4-Trifluoromethyl-phenylamine 1H-cyclopenta[c]quinoline (CRX001016)

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid (CRX000762)

4-Furan-2-yl-8-trifluoromethoxy-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline (CRX000385)

8-Methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline-4-carboxylic acid ethyl ester (CRX000489)

4-Furan-2-yl-8-methyl-2,3,3a,4,5,9b-hexahydro-furo[3,2-c]quinoline (CRX000488)

[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-methanol (CRX000896)

1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanol (CRX000906)

1-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-2,2,2-trifluoro-ethanol (CRX001116)

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid 2,4-dichloro-benzylamide

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid 4-chloro-benzylamide

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid [2-(4-chloro-phenyl)-ethyl]-amide

8-Trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid (2-ethyl-phenyl)-amide

[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yloxy]-acetic acid

2-[4-(2,4-Dichloro-phenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yloxy]-2-methyl-propionic acid

2-[3-Chloro-4-(8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenoxy]-2-methyl-propionic acid

[3-Chloro-4-(8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-phenoxy]-acetic acid

4-(4-Benzyloxy-2-chloro-phenyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

4-(4-Fluoro-2-trifluoromethyl-phenyl)-8-(2,2,2-trifluoro-1-methoxy-1-trifluoromethyl-ethyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

1-[4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-1,2,3,3a,4,9b-hexahydro-cyclopenta[c]quinolin-5-yl]-2,2,2-trifluoro-ethanone

4-(2,4-Dichloro-phenyl)-5-methyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

2,2,2-Trifluoro-1-(8-trifluoromethoxy-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl)-ethanone

5-Benzenesulfonyl-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

5-(2,4-Dichloro-benzyl)-8-trifluoromethoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

2-[5-(2,4-Dichloro-benzyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ol

2,2,2-Trifluoro-1-[8-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl]-ethanone

5-Methyl-8-(2,2,2-trifluoro-1-methoxy-1-trifluoromethyl-ethyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

1-[4-(2,4-Dichloro-phenyl)-8-trifluoromethoxy-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl]-propan-1-one.

4. A LXR agonist having the structure of compound of claims 1 to 3.

5. A pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to any of claims 1 to 4.

6. A pharmaceutical composition according to claim 5, further comprising at least one additional lipid-lowering agent.

7. A compound according to any of claims 1 to 4 or a composition according to claims 5 or 6 for use in the treatment of hyperlipidemia, obesity, type II diabetes, atherosclerosis, ischemic heart disease, peripheral vascular disease, cerebral vascular disease, hypercholesterolemia, hypertriglyceridemia, pancreatitis or coronary artery disease.

8. A method for modulating the LXRs functions in a cell, a tissue and/or a patient in need thereof wherein said cell, tissue or patient is contacted with a sufficient concentration of at least one compound according to any of claims 1 to 4 or a composition according to claims 5 or 6.

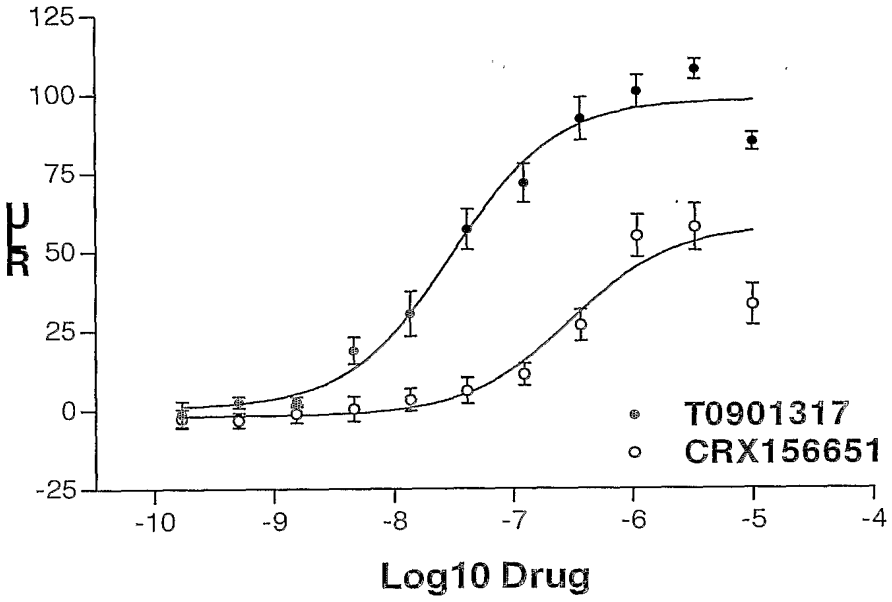


Figure 1

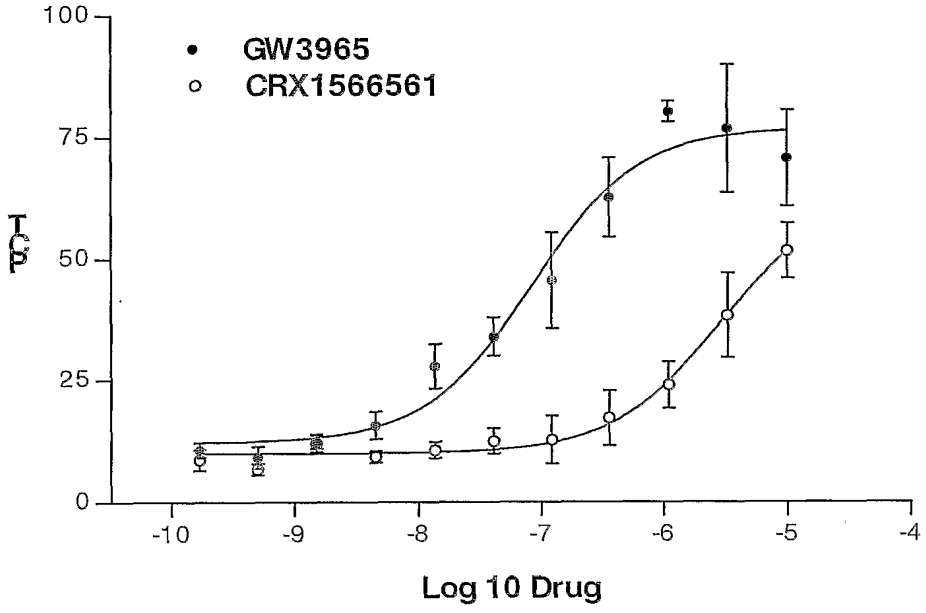
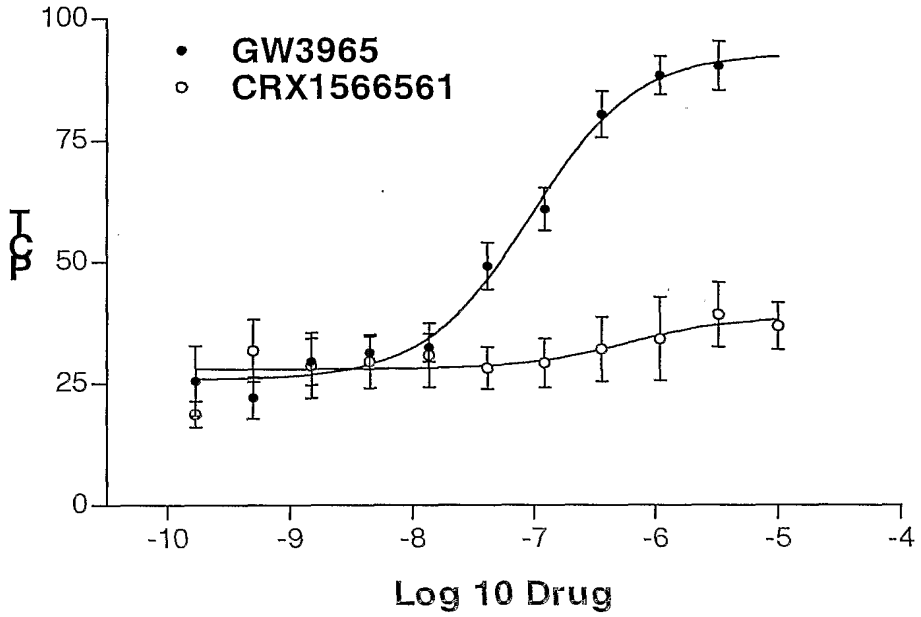


Figure 2

3A



3B

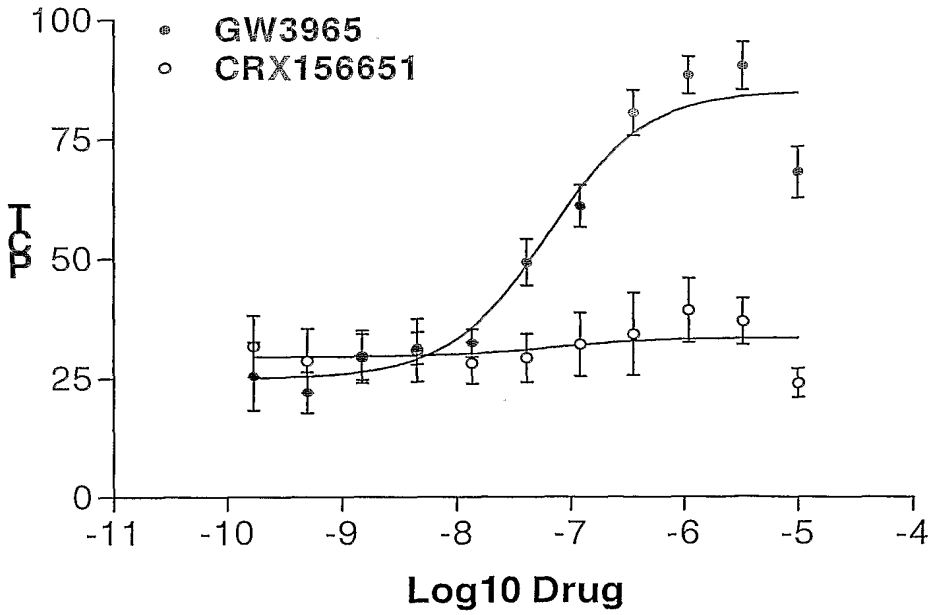


Figure 3

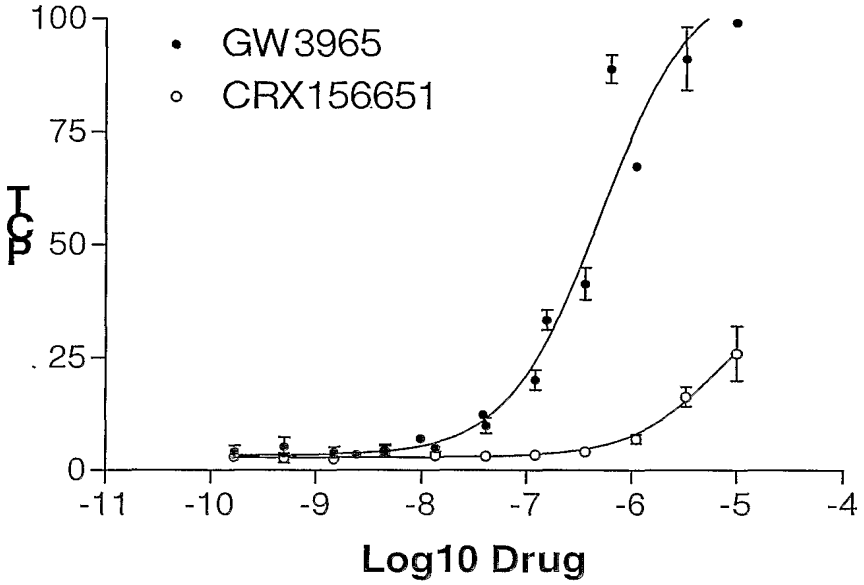


Figure 4

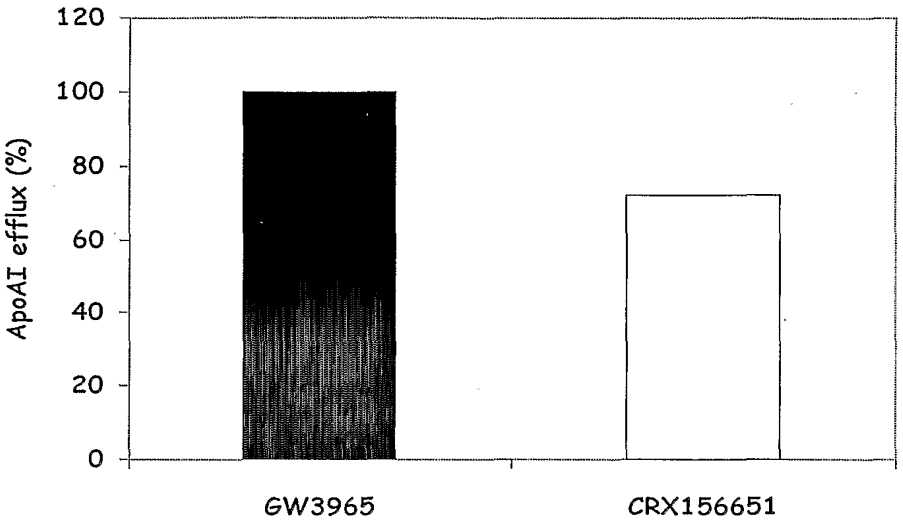


Figure 5

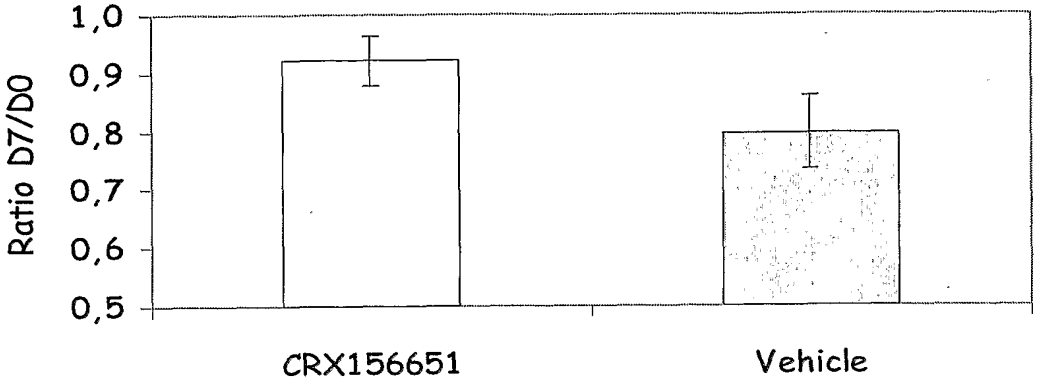
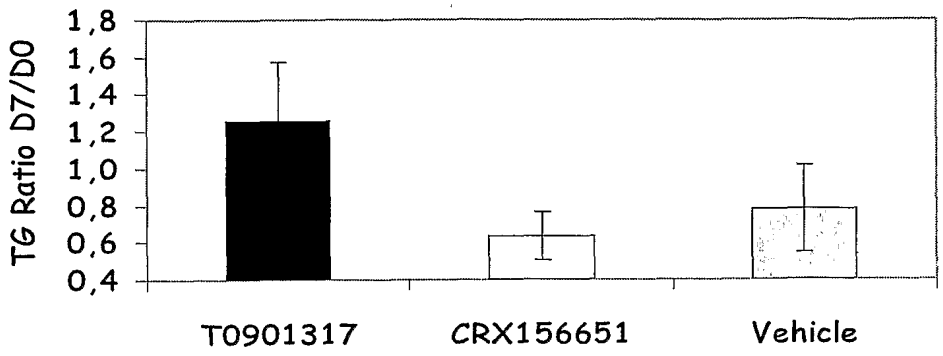


Figure 6

7A



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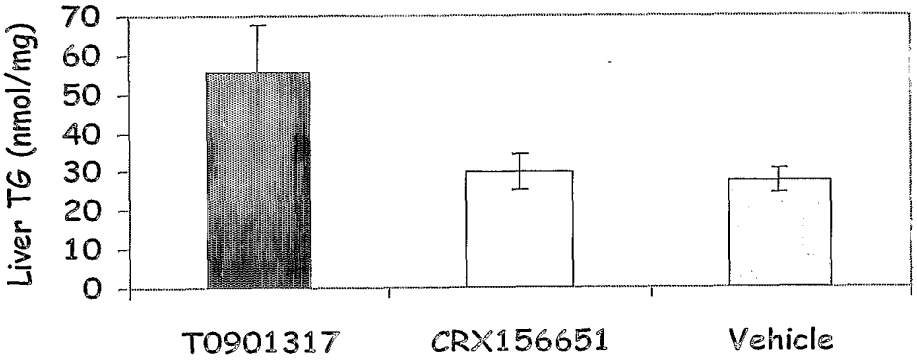

Figure 7